Treatment of ankylosing spondylitis with disease modifying antirheumatic drugs

I.E. van der Horst-Bruinsma[1], D.O. Clegg[2], B.A.C. Dijkmans[1]

[1]*Department of Rheumatology, Vrije Universiteit Medical Centre, Amsterdam, The Netherlands;*
[2]*Division of Rheumatology, University of Utah School of Medicine, Salt Lake City, USA.*

Please address correspondence to: Mrs. I.E. van der Horst-Bruinsma MD, PhD, Vrije Universiteit Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands. E-mail: secr.reumatologie@vumc.nl

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ABSTRACT

Ankylosing apondylitis (AS) is a common (prevalence 0.2–0.9%) chronic inflammatory disease that mainly affects young males and is characterised by inflammatory back pain with sacroiliitis and often arthritis of the peripheral joints. The disease can lead to deformities of the vertebral column, joints and extra-spinal structures, e.g. the eye (uveitis).

Non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy seem to improve the long-term outcome of AS. However, the effect of disease modifying antirheumatic drugs (DMARDs) is less impressive compared with other rheumatic diseases, such as rheumatoid arthritis (RA). In placebo controlled trials, sulfasalazine showed some improvement of disease activity, especially in spondyloarthropathy patients with peripheral arthritis. Altogether the number of therapeutic options for AS is limited and other drugs, such as leflunomide or thalidomide, should be explored further in placebo-controlled trials.

Introduction

Ankylosing spondylitis (AS) is a relatively common chronic inflammatory disorder that mainly affects young males. The disease presents with low back pain and morning stiffness due to sacroiliitis and can result in destruction of the vertebral column leading to postural deformities, like ankylosis of the cervical spine and kyphosis. Extra spinal manifestations of the disease consist of arthritis of the peripheral joints (especially shoulders and hips), resulting in joint destruction that sometimes necessitates joint replacement, uveitis, enthesitis, cardiac and pulmonary complications (1, 2). The diagnosis AS requires fulfilment of the modified New York criteria (3).

The onset of complaints is often gradual and the mean delay is 8 years to the time of diagnosis (2). Until recently, the prevalence was estimated 0.2% in the Caucasian population. However, with more sensitive diagnostic modalities like MRI-scanning, a prevalence up to 0.9% was reported (4).

AS belongs to a group of diseases which are referred to as Spondylarthropathies (SpA). The group of Spondylarthropathies includes rheumatoid factor negative patients with inflammatory back pain and/or asymmetrical synovitis, like psoriatic arthritis, inflammatory bowel disease (e.g. Crohn's disease) and reactive arthritis. The prevalence of SpA is estimated at 1% in the Caucasian population, which equals the prevalence of RA. SpA is diagnosed according to the criteria of the European Spondylarthropathy Study Group (ESSG) (5).

There is an increased prevalence of the Human Leukocyte Antigen (HLA-B27) gene in these disorders. More than 95% of the primary Caucasian AS patients and at least 50% of the psoriatic or inflammatory bowel patients are HLA-B27 positive.

The course of AS is highly variable and characterised by remissions and exacerbations. The erythrocyte sedimentation rate is elevated rate in only 75% of the patients with an exacerbation. The risk of ankylosis of the cervical and thoracic spine increases with a higher disease activity, as well as the risk of joint destruction. Therefore, like in RA, more aggressive treatment seems necessary in order to prevent joint damage and, if possible, spine deformities.

Drug therapy

NSAIDs

There are currently only a few therapeutic options available, such as non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy. High dose NSAIDs, especially the slow release preparations, are very effective in influencing pain and morning stiffness. Phenylbutazone is claimed to be very effective, although there are no com-

parative trials available with other NSAIDs and its is limited by its bone marrow toxicity.

DMARDs

Reports of almost all available DMARDs have been published, but only a few agents designated as DMARDs for RA show some beneficial effects in AS. However, the number of generally accepted double blind, placebo-controlled trials in AS is limited. A few of these drugs may improve peripheral arthritis but there is no evidence that they influence the axial involvement.

Moreover, in contrast with RA, response criteria for the assessment of disease activity, were only recently developed in AS by the Assessment in Ankylosing Spondylitis working group (ASAS) (6,7). Most studies were based on separate outcome measures like the Bath Ankylosing Spondylitis Functional Index (BASFI) (8), pain (Visual Analogue Scale, VAS), spinal stiffness (VAS), fatigue (VAS), general well being according to the patient and physician (VAS), mobility (Bath Ankylosing Spondylitis Metrology Index) (9), peripheral joint swelling and laboratory tests like ESR and CRP. A few studies used a composite index like the Bath Ankylosing Spondylitis Disease activity Index (BASDAI) (10).

Sulfasalazine

In 1984,Amor *et al.* (11) suggested that sulfasalazine may be effective in ankylosing spondylitis, particularly in patients with peripheral arthritis. Subsequently, a number of other double-blind placebo-controlled trials (12-15) have been published with controversial results. Sulfasalazine consistently reduces erythrocyte sedimentation rates and C-reactive protein levels. Data regarding the potential benefit of sulfasalazine on clinical symptoms or signs of disease are less definitive. An improvement of disease activity, including spinal mobility, was observed in another study of 85 AS patients treated with sulfasalazine compared to placebo (15). Ferraz *et al*. (16) reported a meta-analysis of five randomised controlled trials. The results of this analysis indicated that sulfasalazine had clinical benefit over placebo in duration of morning stiffness, severity of morning stiffness, severity of pain, and general well-being, erythrocyte sedimentation rate, and serum IgA values. Even though efficacy data regarding sulfasalazine in AS are unclear, the medication is well tolerated (17, 18). Mild gastrointestinal intolerance, including nausea and anorexia, is the most commonly reported symptom. In addition, minor skin rashes are reported with some frequency. Much less frequently reported abnormalities include liver function aberrations, hematologic abnormalities, such as agranulocytosis, hemolytic anemia, and thrombocytopenia, and neurologic effects, including dizziness, headache, and vertigo. Sulfasalazine has been studied in divided doses of 2 to 3 g per day. Blood counts and chemistries should initially be monitored at twice monthly intervals to detect cytopenias; however, once a patient is successfully tolerating the medications, toxicity surveillance can be modified after several months.

In summary, sulfasalazine may have a place in the treatment of ankylosing spondylitis. It appears likely that the potentially beneficial effects of sulfasalazine are in the treatment of the peripheral arthritis associated with AS (19). There have been no studies to evaluate its long-term potential as a "disease-modifying" agent. The recommended daily dose is 30 to 40 mg/kg/day.

Mesalazine

To assess the active moiety of sulfasalazine, Taggert *et al.* (17) studied three groups of 30 AS patients, one with sulfasalazine, the second with 5-aminosalicylic acid (Asacol®, ASA, 800 mg) and the third with sulfapyridine (1.25 gram). The number of premature discontinuations was high in each of the three groups, especially in the ASA group (24 out of 34). The conclusion was that there was no important change in the outcome parameters of the three groups.

Mesalazine (or 5-acetylsalacylic acid (5-ASA) might be also the effective component of sulfasalazine. This medication, which is proven to be effective in inflammatory bowel disease, was investigated in an open non-controlled study in 39 SpA-patients (20). Improvement of the physicians global clinical assessment was observed in 85% of the patients. The number of side effects was very low.

Another study, performed in 30 SpA-patients, showed statistically significant improvement of clinical, physical and laboratory parameters with a dosage of 1500-4000 mg/day (21).

Recently, another open study (22) with mesalazine (Salofalk®) in 20 AS patients during 24 weeks did not show any favourable results. There was no change in BASDAI, BASFI nor in the BASMI. The number of side effects was high, especially the gastrointestinal complaints.

It can be concluded that mesalazine does not seem to be effective in AS.

Methotrexate

Methotrexate (MTX), a DMARD that is very effective in rheumatoid arthritis and psoriatic arthritis, is less commonly used in AS. Unfortunately, there have been no controlled trials using MTX in AS, only some small open studies with low doses MTX.

A few older reports, including one case report, show the beneficial effect of MTX in AS (23,24). In a small open study in 15 Turkish AS patients were treated with a low dose MTX (7.5 mg/week) combined with Indomethacin (175 mg/day) and showed improvement of disease activity without any side effects (25). The efficacy of the same dose of MTX in combination with Naproxen 1000 mg/day was compared with Naproxen alone in 51 AS patients (26). This combination was not superior to the treatment with Naproxen alone, which is probably due to the low dose of MTX used. This dose effect is supported by the observation of Sampaio-Barros (27) who more successfully treated 34 AS patients with a weekly intramuscular dose of 12.5 mg MTX during one year, which resulted in a good response in 53% of the patients, with a decline in ESR and peripheral arthritis. In a 3 year open trial with only 17 patients and a MTX-dosage of 7.5–10 mg/week (28) with improvement of well being and physical function and a decrease in ESR and CRP-levels. Two open studies (29, 30),

with only 11 and 9 patients respectively, also showed beneficial effects of oral 7.5–15 mg MTX weekly.
However, all these data have a limited scientific relevance because these studies are small and not placebo-controlled.

Leflunomide
The fact that many patients suffering from RA respond favourably to treatment with leflunomide offers an opportunity for improvement of the outcome in AS.
In patients with psoriatic arthritis successful interventions were recently published showing an improvement of skin involvement as well as in arthritis. However, there are no data indicating improvement in axial disease in psoriatic arthritis patients nor have intervention trials in AS been reported.

Azathioprine
Azathioprine is seldom used in AS, but recently one study was published that compared azathioprine with sulfasalazine in 32 AS patients (31). In this double blind study patients were randomised to 2–3 gram/day sulfasalazine or 100–150 mg/day azathioprine. 12 of the 18 azathioprine treated patients were withdrawn because of the side effects. Four of the 6 remaining patients showed 25% response of the BASDAI. Most of the sulfasalazine treated patients who were on remained in the study and showed a response in 66%.
Therefore it was concluded that azathioprine was less well tolerated than sulfasalazine in AS.
One case report (32) described a dramatic response on an intravenous loading dose (40 mg/kg) followed by an oral therapy with 2 mg/kg in a refractory case of AS.

Corticosteroids
Orally administered corticosteroids do not show beneficial effects in AS. Intravenous pulse therapy with methylprednisolone (1000 mg) showed a temporarily relief of pain and improvement of mobility during 6 weeks in a small number of patients (33, 34). The efficacy of a high dose (1000 mg) though was not significantly better than of a lower dose (375 mg) (35).
However, this therapy carries the risk of severe side effects, such as osteonecrosis of the femoral head and sudden death. Nasswetter *et al.* (36) studied this risk factor in 5 AS patients but observed no cardiovascular symptoms during infusion with methylprednisolone.
Injections in the sacroiliac joints are proven to be ineffective in inflammatory spondylarthropathy (37), although some uncontrolled studies (38, 39)suggest the opposite.
Intra-articular injections with local corticosteroids are effective in case of peripheral arthritis.

Other DMARDs
To our knowledge, no reports on the efficacy combination therapies were found in AS, in contrast with RA, except for one abstract (40) which describes combination strategies in spondylarthropathy. In this study 3 groups of SpA-patients and peripheral joint involvement were treated with either sulfasalazine alone (1-2 gram/day), sulfasalazine in combination with methotrexate (7.5 – 15 mg/week) or both sulfasalazine and methotrexate plus hydroxychloroquine 200 mg/day. After 2 years more improvements were observed with combination therapies, especially in the third group.
The effect of other second-line drugs used in RA has not evaluated in placebo-controlled trials, but some anecdotal reports show little improvement of these therapies.
Auranofin. Grasedyck *et al.* (41) reported a series of patients in whom auranofin produced no improvement in the disease manifestations of AS.
D-penicillamine was tested in Poland (42) in 49 AS patients and this open study showed beneficial effects on the peripheral as well as the central lesions. In contrast, a placebo-controlled trial did not show any significant improvement of D-penicillamine over placebo (43).
Cyclophosphamide, given intravenously 200 mg/2 days during 3 weeks, followed by an oral dose of 100mg/day showed improvement of peripheral arthritis and ESR in an open study of 12 patients (44).
As far as we know, only one case report refers to the efficacy of **cyclosporine** (4 mg/kg/day) in AS, which was effective in the control of peripheral arthritis (45).
Pamidronate. In an open study (46) of 16 patients with refractory ankylosing spondylitis who received intravenous pamidronate, improvement was noted in some of the outcome measures and further evaluation in a controlled setting was recommended.
Some small open studiesand a few case reports (47-49) describe that thalidomide is effective in AS, despite frequent side effects. Recently, an open study (50) with 30 male AS patients showed a significant improvement after 3 months treatment with 200–300 mg thalidomide per day. The efficacy is probably due to the inhibition of tumour necrosis factor alfa production, which is supported by the therapeutic successes of infliximab (51, 52) and etanercept (53) in AS.

Conclusion
In contrast with rheumatoid arthritis, only a few DMARDs show a beneficial clinical effect in ankylosing spondylitis, and the number of placebo-controlled trials is limited. There have been no trials using these medications in ankylosing spondylitis that have shown any evidence of actual disease modification. Sulfasalazine shows some improvement, especially in case of peripheral arthritis. Further exploration of the efficacy of thalidomide, leflunomide and combination therapies in AS might improve the outcome of this disease in the future. Exciting advances from emerging data that suggest efficacy of other agents that inhibit TNF activity such as infliximab and etanercept are discussed elsewhere in this monograph.

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