

## REVIEW

# Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis

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**Objective:** To assess available management strategies in ankylosing spondylitis (AS) using a systematic approach, as a part of the development of evidence based recommendations for the management of AS. **Methods:** A systematic search of Medline, Embase, CINAHL, PEDro, and the Cochrane Library was performed to identify relevant interventions for the management of AS. Evidence for each intervention was categorised by study type, and outcome data for efficacy, adverse effects, and cost effectiveness were abstracted. The effect size, rate ratio, number needed to treat, and incremental cost effectiveness ratio were calculated for each intervention where possible. Results from randomised controlled trials were pooled where appropriate.

**Results:** Both pharmacological and non-pharmacological interventions considered to be of interest to clinicians involved in the management of AS were identified. Good evidence (level Ib) exists supporting the use of non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs for symptomatic treatment. Non-pharmacological treatments are also supported for maintaining function in AS. The use of conventional antirheumatoid arthritis drugs is not well supported by high level research evidence. Tumour necrosis factor inhibitors (infliximab and etanercept) have level Ib evidence supporting large treatment effects for spinal pain and function in AS over at least 6 months. Level IV evidence supports surgical interventions in specific patients.

**Conclusion:** This extensive literature review forms the evidence base considered in the development of the new ASAS/EULAR recommendations for the management of AS.

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease most commonly affecting the axial skeleton, which historically has been difficult to treat. Recent years have seen the introduction of exciting new therapeutic strategies, particularly the tumour necrosis factor inhibitors. Therefore it is important that clinicians are aware of the relative benefits and risks of the different treatments available to them, and have evidence based information about which strategies are the most efficacious in particular patient settings.

The ASsessment in AS (ASAS) International Working Group, in collaboration with the European League Against Rheumatism (EULAR), recently developed evidence based recommendations for the management of AS<sup>1</sup> to assist all health professionals involved in the care of patients with AS.

The recommendations were developed using information from two major sources: a systematic review of the literature, and expert opinion based on the research evidence and clinical expertise.<sup>1</sup> This review details the literature search performed and the results presented to the expert committee for the purpose of developing recommendations for the management of AS.

## METHODS

A systematic search of the literature published between January 1966 and December 2004 was undertaken using Medline, Embase, CINAHL, PEDro, and Cochrane Library databases. The search included both a general search and an intervention-specific search. The general search strategy consisted of two basic components: AS in whatever possible terms in the databases (Appendix 1) and types of research in

the form of systematic review/meta-analysis, randomised controlled trial (RCT)/controlled trial, uncontrolled trial, cohort study, case-control study, cross sectional study, and economic evaluation (Appendix 2). The general search aimed at summarising the current available treatments from the literature for AS. The summary results of this search were reported to the ASAS/EULAR expert committee at the beginning of the recommendation development process.

After the expert group had generated 10 recommendation propositions, an intervention-specific search was undertaken to identify evidence for each specific treatment. The search strategy included the terms for AS (Appendix 1) and any possible terms for the specific intervention. The results of the two searches were then combined and duplications excluded. Medical subject heading (MeSH) search was used for all databases and keyword search was used if the MeSH search was not available. All MeSH search terms were exploded. The reference lists of reviews or systematic reviews were examined and any additional studies meeting the inclusion/exclusion criteria were included.

The search in the Cochrane Library included a MeSH search of the Cochrane reviews, abstracts of Quality Assessed Systematic Reviews, the Cochrane Controlled Trial Register, NHS Economic Evaluation Databases, Health Technology

**Abbreviations:** AS, ankylosing spondylitis; ASAS, ASsessment in AS; CI, confidence interval; DMARDs, disease modifying antirheumatic drugs; ES, effect size; GI, gastrointestinal; IV, intravenous; MeSH, medical subject heading; NNT, number needed to treat; NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomised controlled trial; RR, relative risk; THR, total hip replacement; TNF, tumour necrosis factor

Assessment Database, and NHS Economic Evaluation Bibliography Details Only. Abstracts of scientific meetings held in 2003 and 2004 and "online first" publications were also hand searched for relevant studies.

### Inclusion/exclusion criteria

Only studies with clinical outcomes for AS were included. The main focus of interest was on systematic reviews, RCTs/controlled trials, uncontrolled trials/cohort studies, case-control studies, cross sectional studies, and economic evaluations. Studies that included patients with AS in a larger cohort of different spondyloarthritides (for example, psoriatic arthritis) were excluded unless the results for patients with AS were reported separately. Studies of other seronegative spondyloarthritides or other inflammatory joint conditions, animal studies, non-clinical outcome studies, narrative review articles, commentaries, and guidelines were also excluded.

### Categorising evidence

Evidence was categorised according to study design using a hierarchy of evidence in descending order according to qualities<sup>2</sup> (table 1), and the highest level of available evidence for each intervention was reviewed in detail. When very few high level studies were available, the next highest category was also reviewed. The most recent meta-analysis of RCTs (level Ia) was reviewed for each intervention, and any RCTs published since the meta-analysis was conducted were also considered.

Efficacy was assessed specifically for AS, and toxicity data were evaluated specifically for the intervention, irrespective of the musculoskeletal condition.

### Estimation of effectiveness and cost effectiveness

Effect size (ES, mean change divided by the standard deviation of the change) and 95% confidence interval (95% CI) compared with placebo or active control were calculated for two predetermined continuous outcomes: pain relief and improvement in function.<sup>3</sup> The percentage of patients with an ASAS20 response to treatment, or with moderate to excellent (predefined as more than 50%) pain relief or moderate functional improvement (predefined as more than 20%) was calculated where possible, and the number needed to treat (NNT) was estimated for these dichotomous outcomes.<sup>4</sup> The NNT is the number of patients who need to be treated with a given intervention in order to prevent one poor outcome, and is the inverse of the absolute risk reduction. Results from the latest systematic review were used if there was more than one systematic review for the same intervention. Statistical pooling was undertaken as appropriate<sup>5</sup> when a systematic review was not available, or when more recent RCTs could be

included. The NNT and 95% CI were reported only if statistically significant; otherwise "NS" (not significant) was used to avoid difficulty in interpreting the results.<sup>6</sup> Relative risk (RR) was calculated for adverse effects.

When economic evaluation was available, study design, comparator, perspective, time horizon, discounting, total costs, and effectiveness were reviewed. The incremental cost effectiveness ratio was calculated. Quality of life years were used when available, otherwise disease-specific outcomes such as pain relief and functional improvement were used.

Data were extracted by one investigator (JZ). A customised form was used for the data extraction.

## RESULTS

### Treatment modalities and types of research evidence

The general search yielded 4100 hits (Medline 2395, Embase 1581, CINAHL 73, PEDro 16, and Cochrane 35). After deleting duplications, non-treatment studies, and studies of diseases other than AS, 458 hits remained. Of these, 318 were original studies and 140 were narrative reviews, commentaries, or editorials. Figure 1 shows the breakdown of interventions among the original 318 studies. Of these studies, 35 were RCTs, 7 were systematic reviews, and 4 were economic evaluations.

The results from the intervention-specific search were merged with the results from the general search. After deleting the duplications and articles irrelevant to the questions (for example, studies on radiation therapy), 317 studies remained for review. These included: 73 related to non-pharmacological treatments; 55 associated with NSAIDs or coxibs; 61 in relation to conventional anti-rheumatoid arthritis drugs; 8 for bisphosphonate treatment; 6 for thalidomide; 15 for corticosteroids (intravenous or intra-articular); 64 for biological treatments; and 55 relevant to total hip replacement or spinal surgery.

The evidence for each intervention relevant to the ASAS/EULAR recommendations, as presented to the expert group, is discussed below.

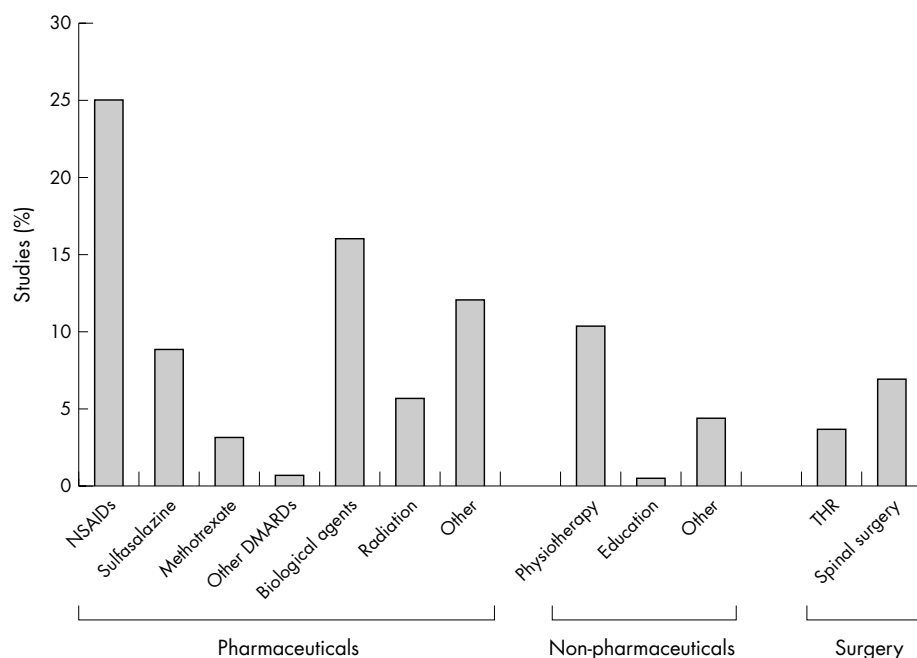
### Non-pharmacological treatment

#### Physiotherapy and exercise

The effect of physiotherapy has recently been reviewed in a Cochrane systematic review<sup>7</sup> summarising the findings of six randomised or quasi-randomised trials. Of the studies included, Kraag *et al* reported that an individual programme of therapeutic exercise combined with education and disease information significantly improved function at 4 months (ES 1.14, 95% CI 0.55 to 1.73) compared with no intervention.<sup>8</sup> There was no significant effect on pain levels. After the 4 month trial, this improvement in function was maintained

**Table 1** Evidence hierarchy and traditional strength of recommendation

Category of evidence	Strength of recommendation
Ia Meta-analysis of randomised controlled trials	A Category I evidence
Ib Randomised controlled trial	
IIa Controlled study without randomisation	B Category II evidence or extrapolated from category I evidence
IIb Quasi-experimental study	
III Non-experimental descriptive studies, such as comparative, correlation, and case-control studies	C Category III evidence or extrapolated from category I or II evidence
IV Expert committee reports or opinion or clinical experience of respected authorities, or both	D Category IV evidence or extrapolated from category II or III evidence



**Figure 1** Interventions for AS from the general literature search.

by minimal continuing treatment (1.5 mean visits from the physiotherapist between month 4 and month 8).<sup>9</sup>

Hidding *et al* compared group physical therapy and home exercises with home exercises alone, after an intensive training programme for both groups, and found that although pain and functioning improved significantly in both intervention groups, there was no significant difference between the groups for these two outcome measures.<sup>10</sup> Patient global assessment of improvement and spinal mobility were seen to be statistically higher in the group physiotherapy arm ( $p < 0.05$ ). Cost effectiveness analysis of these patients<sup>11</sup> showed that each centimetre of visual analogue scale improvement cost \$292 over 1 year.

A third study compared intensive inpatient physiotherapy, hydrotherapy with home exercises, and home exercise alone, but did not specify pain or function as separate outcome variables.<sup>12</sup> This study showed significant short term improvement in composite pain and stiffness in the inpatient treatment group at 6 weeks, but there was no difference between the three groups at 6 months. Comparison of an intensive group exercise programme with unsupervised home exercise<sup>13</sup> found that neither pain nor function was significantly better in the group physiotherapy arm than in the home exercise arm. A home based exercise and education package was not shown to improve pain or function compared with controls over 6 months.<sup>14</sup> However, a recent small RCT of home exercise not included in the Cochrane review showed significant improvements after 8 weeks in both pain (ES 1.99, 95% CI 1.30 to 2.67) and function (ES 0.80, 95% CI 0.23 to 1.38) in young patients with AS (mean age 28 years) who had previously been sedentary.<sup>15</sup> It was not possible to pool the results of separate studies owing to differing interventions and outcome measures. The literature suggests that different types of exercise based intervention can impact on disease outcomes in AS, which might account for the lack of significant differences between treatment arms in the absence of a placebo/no treatment arm.

Specific physiotherapy interventions have been less well studied in AS. One randomised controlled trial comparing transcutaneous electrical nerve stimulation (TENS) with sham TENS treatment over 3 weeks reported a significant short term improvement in pain in the treatment arm<sup>16</sup>;

however, when the data were reanalysed the ES of 0.92 did not reach statistical significance (95% CI  $-0.01$  to  $1.86$ ,  $p = 0.05$ ). Passive stretching has been shown in a controlled study to improve range of movement at the hip,<sup>17</sup> but pain and function were not assessed. Pulsed magnetic fields may have an effect on pain, as shown in a small open study of seven patients with AS who were intolerant of non-steroidal anti-inflammatory drugs (NSAIDs).<sup>18</sup> Level Ib evidence does not support the use of heat or whole-body cryotherapy.<sup>19</sup> A number of open studies (level IV evidence) have shown variable results for spa treatment.<sup>20-23</sup> The only randomised controlled trial identified looked at the effect of a 3 week spa exercise programme followed by weekly group physiotherapy sessions, compared with group physiotherapy alone.<sup>24</sup> Function was seen to be significantly improved in the spa groups at 4 and 12 weeks ( $p < 0.01$ ), but the effect of treatment on pain or function was not significantly different between the groups at the end of the 40 week study period. A cost effectiveness analysis of this cohort<sup>25</sup> showed an incremental cost effectiveness ratio of €7465 to €18 575 for each quality of life year gained over the trial period.

### Education

The effect of isolated education for AS is not clear. There has been one controlled study of self management courses for patients with AS,<sup>26</sup> which showed early improvements in functioning in the treatment group after 3 weeks, but failed to show significant improvements in pain or function compared with controls at 6 months. Importantly, education brought considerable improvements in self efficacy and motivation. A small controlled trial of cognitive behavioural therapy targeting relaxation, modifying thoughts and feelings, and scheduling positive activities<sup>27</sup> failed to show any significant improvements in pain (ES 0.53, 95% CI  $-0.07$  to  $1.13$ ); however, there was a convincing improvement in anxiety (ES 1.11, 95% CI 0.48 to  $1.75$ ). Cost analysis of a patient education programme over 12 months suggests that indirect cost savings more than compensate for the costs of the programme through a reduction in work days lost.<sup>28</sup> There are no clinical studies of the effect of participation in an AS self help group on disease parameters. Vocational rehabilitation is effective in returning patients with chronic rheumatic

diseases to work,<sup>29</sup> but studies do not distinguish between diseases.

### Lifestyle modification

There is little available evidence to support lifestyle modification in AS. Stopping smoking may be of benefit; three cross sectional studies have shown a poorer functional outcome in patients with AS who smoke,<sup>30–32</sup> but there have not been any interventional studies to support this observation. A low starch diet was effective in reducing pain in one case study,<sup>33</sup> but the only open study available did not report pain or function as outcomes.<sup>34</sup> A small case-control study of dairy restriction in patients with arthritis showed that significantly more patients with SpA than those with RA ( $p < 0.001$ ) reported moderate or good subjective improvement.<sup>35</sup>

### NSAIDs and coxibs

Eight randomised, placebo controlled trials were identified, all of which supported the use of NSAIDs or coxibs for pain in AS.<sup>36–43</sup> Pooling of results was possible for four NSAID trials, three of which compared a conventional NSAID with a coxib in addition to the placebo arm.<sup>41–43</sup> There is thus convincing level Ib evidence that NSAIDs improve spinal pain compared with placebo (ES 1.11, 95% CI 0.96 to 1.26), peripheral joint pain (ES 0.62, 95% CI 0.26 to 0.97, reported in only one study<sup>36</sup>), and function (ES 0.62, 95% CI 0.47 to 0.76) over a short time period (6 weeks). Coxibs are equally effective, the ES for spinal pain 1.05 (0.88 to 1.22) and for function 0.63 (0.47 to 0.80), also showing moderate to large effects in patients with AS compared with placebo. The effect of coxibs on peripheral arthritis has not been specifically investigated in AS; all studies have excluded patients with active peripheral synovitis. A post hoc analysis of etoricoxib in patients with AS with chronic peripheral arthritis compared with spinal disease alone suggests poorer spinal response rates in patients with arthritis.<sup>44</sup> Most RCTs of NSAID treatment in AS compare different NSAID compounds, with no clear indication that any one preparation is more efficacious than the others.<sup>45–70</sup>

Safety concerns associated with NSAIDs and more recently with coxibs must, however, be considered. The recent EULAR recommendations for the management of hip osteoarthritis<sup>71</sup> include an extensive review of the gastrointestinal (GI) toxicity of anti-inflammatory agents; in short, NSAIDs cause an increased risk of GI bleeding,<sup>72–77</sup> which is dose dependent,<sup>75</sup> and can be reduced with gastroprotective agents such as misoprostol, double doses of H<sub>2</sub> blockers, and proton pump inhibitors.<sup>78–82</sup> Severe GI toxicity (peptic ulceration and bleeding) has been shown to be lower with coxibs,<sup>83</sup> although there remains a considerable risk of GI symptoms including dyspepsia and diarrhoea.

Cardiovascular toxicity with coxibs and NSAIDs has become very topical, and what began initially as a safety signal with rofecoxib has now been seen with other coxib preparations and, most recently, with traditional NSAIDs. The most recent meta-analysis of RCTs of rofecoxib<sup>84</sup> calculated the relative risk for myocardial infarction with rofecoxib as 2.30 (95% CI 1.22 to 4.33) compared with placebo. Analysis of preliminary 3 year data from the Adenomatous Polyposis Prevention with Vioxx (APPROVE) study<sup>85</sup> showed an increased risk of serious thromboembolic events, including myocardial infarction or stroke in the rofecoxib treated group after 18 months of chronic dosage (RR 1.92, 95% CI 1.19 to 3.11), and led to the removal of rofecoxib from the market. Preliminary results of one of two long term cancer prevention studies have subsequently shown celecoxib to be associated with a dose related increase in cardiovascular risk compared with placebo,<sup>86</sup> and valdecoxib was associated with an increased risk (RR 3.7, 95% CI

1.0 to 13.5) of serious cardiovascular outcome in patients with a coronary artery bypass graft compared with placebo.<sup>87</sup> In short, cardiovascular toxicity seems to be a class effect of the coxibs. This may well not be the end of the story, however; concerns were recently raised after preliminary data from the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) suggested a 50% higher risk of myocardial infarction and stroke in naproxen treated patients compared with placebo (unpublished data). The subject of cardiovascular toxicity with traditional NSAIDs is evolving, and continuing research will hopefully clarify the increased risk which may be associated with NSAID use.

### Simple analgesics

There is no disease-specific evidence to support the use of paracetamol or other analgesics in AS. One small cross sectional study using mail-out questionnaires found that in 15 patients with AS who took both simple analgesics and NSAIDs for their disease, 13 (87%) patients felt that simple analgesics were less effective than NSAIDs,<sup>88</sup> but the question has not been assessed in a prospective manner.

### Local and systemic corticosteroids

Intra-articular steroid injections have been shown to be effective for sacroiliitis (level Ib evidence), with a small randomised placebo controlled trial showing an improvement in pain of 1.94 (95% CI 0.53 to 3.35).<sup>89</sup> Periarticular corticosteroid injection around the sacroiliac joint has also been shown to be effective,<sup>90</sup> responses persisting for at least 8 weeks ( $p = 0.02$ ). There are no clinical studies on the efficacy of intra-articular steroid on peripheral arthritis or enthesitis in AS. One observational study of 51 patients with early oligoarthritis (median disease duration 16 weeks) has shown that intra-articular treatment is effective, improving disease activity as measured by the Health Assessment Questionnaire, swollen joint count, and patient's global pain and disease activity assessments<sup>91</sup>; however, by the end of the study no patient had been diagnosed with AS (26 remained undifferentiated oligoarthritis). There have been no clinical trials on the use of local corticosteroid injections for the enthesitis of AS.

Intravenous methylprednisolone has been described as useful in recalcitrant cases of severe, active AS (level IV evidence).<sup>92–95</sup> No studies evaluating the effect of oral corticosteroid treatment in AS have been published.

### Disease modifying antirheumatic drugs (DMARDs) Sulfasalazine

Sulfasalazine has inconclusive level Ia evidence for efficacy in AS. The most recent meta-analysis<sup>96</sup> reviewed 12 randomised controlled trials in active AS, and concluded that there is no evidence for a clinically relevant benefit on spinal symptoms or function, but sulfasalazine may have a role in peripheral joint disease associated with spondyloarthritis. When data from the individual trials were pooled, the effect on back pain (ES -2.38, 95% CI -5.78 to 1.03) or physical function (ES 0.20, 95% CI -0.77 to 1.18) with sulfasalazine compared with placebo was not significant. Two studies described combined groups of patients with spondyloarthritis without reporting results in AS separately. Dougados *et al* found a significant improvement in swollen joint count in patients treated with sulfasalazine ( $p = 0.002$ ),<sup>97</sup> and Clegg *et al* showed that improvements in patient global assessments were more marked in the subgroup of patients with peripheral joint involvement.<sup>98</sup> In the only extended AS trial reviewed,<sup>99</sup> patients treated with sulfasalazine over 3 years had significantly fewer episodes of peripheral joint symptoms than those receiving placebo ( $p < 0.05$ ). There is level IV evidence against an effect of sulfasalazine on enthesitis in spondyloarthritis.<sup>100</sup> A pilot



study of 5-aminosalicylic acid (thought to be the active moiety in sulfasalazine) in AS showed improvements in investigator global assessment and erythrocyte sedimentation rate, but did not examine pain or function separately.<sup>101</sup>

Toxicity with sulfasalazine is common (RR for any adverse event 2.37, 95% CI 1.58 to 3.55)—usually gastrointestinal symptoms, mucocutaneous manifestations, hepatic enzyme abnormalities, and haematological abnormalities.

### Methotrexate

One systematic review has been published on the use of methotrexate in AS.<sup>102</sup> This reviewed two RCTs, one in 51 patients comparing methotrexate 7.5 mg orally a week in combination with naproxen 1000 mg orally daily with naproxen 1000 mg orally daily alone,<sup>103</sup> and a second in 30 patients comparing methotrexate 10 mg orally a week with placebo.<sup>104</sup> Outcome measures differed substantially between the two studies, and so pooling of results was not possible. The authors concluded that there was no evidence to support the use of methotrexate in AS. Since that publication, there has been one further RCT reporting methotrexate 7.5 mg orally a week compared with placebo in only 35 patients.<sup>105</sup> The cohort had a much higher prevalence of peripheral arthritis than the previous two studies (60% v 12% and 30%). Although significant improvements in the Bath AS Disease Activity Index (BASDAI), spinal pain and the Bath AS Functional Index (BASFI) were seen in the treatment arm, there was no significant difference in effect compared with placebo. Pooling results<sup>103 105</sup> gave an effect size for spinal pain of  $-0.05$  (95% CI  $-0.48$  to  $0.38$ ) and for function of  $0.02$  (95% CI  $-0.40$  to  $0.45$ ), neither of which reached statistical significance. Roychowdhury *et al* are the only group to report separate outcomes for patients with peripheral joint involvement, subgroup analysis failing to show any improvement in disease activity with methotrexate in patients with peripheral arthritis, although numbers were small ( $n = 9$ ).<sup>104</sup> There has been one controlled trial, published in abstract form,<sup>106</sup> reporting significant improvement in the number of swollen joints in patients with AS with peripheral arthritis with methotrexate 7.5 mg orally a week, NSAID, and physiotherapy ( $p < 0.0001$ ), but results of comparison with the control group of NSAID and physiotherapy alone were not given.

Five meta-analyses of RCTs of methotrexate treatment<sup>102 107–110</sup> included toxicity data. The most commonly reported side effects of methotrexate treatment at doses equivalent to those used in rheumatological practice include nausea (RR 2.12, 95% CI 1.50 to 2.98) and hepatic abnormalities (RR 4.12, 95% CI 2.22 to 7.63). Other common adverse events recognised at higher doses did not occur significantly more often with treatment than in controls. Ortiz reported a meta-analysis of the use of folate and/or folic acid in conjunction with low dose methotrexate treatment in rheumatoid arthritis, and concluded that folate is effective in preventing GI and mucocutaneous adverse events (RR 0.56, 95% CI 0.38 to 0.80),<sup>111</sup> but there was no convincing evidence to support the use of folic acid (RR 0.66, 95% CI 0.39 to 1.12). In patients with AS, an observational study of stopping treatment owing to drug toxicity<sup>112</sup> found that 21% of patients had stopped methotrexate treatment by 12 months because of significant adverse events ( $n = 14$ ).

### Pamidronate

Intravenous pamidronate has been studied in open trials,<sup>113–116</sup> with contradictory results. The best available evidence is level III<sup>117</sup>—a comparative RCT of 60 mg intravenous (IV) pamidronate against 10 mg IV pamidronate, which supports the use of higher dose bisphosphonate for function (ES 0.73,

95% CI 0.29 to 1.17) and for axial pain ( $p = 0.003$ , insufficient data given to calculate ES). The authors comment that the study was not powered to show any effect on peripheral arthritis. Further RCTs are needed to answer this question. The most commonly reported side effects of IV pamidronate are transient post-infusional arthralgias and myalgias (in up to 78% of patients in observational studies<sup>114 117 118</sup>) and an acute phase response with lymphopenia and raised C reactive protein,<sup>119</sup> which rarely lead to treatment discontinuation.

### Thalidomide

Thalidomide is receiving increasing attention as a possible treatment for severe AS; to date there have been two open trials published showing significant improvement in axial pain and function,<sup>120 121</sup> but effects on peripheral disease have not been reported. Toxicity is substantial, open studies showing consistent problems with drowsiness, dizziness, dry mouth, headache, constipation, and nausea (all  $>15\%$  incidence rates) and high rates of treatment withdrawal due to side effects.

### Other traditional DMARDs used in RA

There is little evidence to support the use of the DMARDs that are used in rheumatoid arthritis in AS. Single case studies support the use of ciclosporin<sup>122</sup> and azathioprine.<sup>123</sup> There are no studies of efficacy for hydroxychloroquine on musculoskeletal disease in AS, although one case study reports a good result in AS associated iridocyclitis.<sup>124</sup> Auranofin treatment was not clinically effective in the only retrieved controlled trial,<sup>125</sup> although the study was too small to reflect an effect on the subgroup of patients with peripheral joint disease. Intravenous cyclophosphamide may be effective in severe, active disease associated with peripheral arthritis,<sup>126 127</sup> supported by level IV evidence. The only RCT of leflunomide in AS<sup>128</sup> failed to show a significant effect on pain (ES 0.14, 95% CI  $-0.48$  to  $0.76$ ) or function (ES  $-0.10$ , 95% CI  $-0.72$  to  $0.52$ ), but was not powered to see any effect on peripheral arthritis, which had been suggested to respond to treatment in an earlier open study.<sup>129</sup> Similarly, one RCT of D-penicillamine in AS was retrieved,<sup>130</sup> which found no effect of treatment on pain (level Ib), and case series of peripheral arthritis in AS have failed to show any benefit.<sup>131 132</sup>

### Biological treatments

#### Tumour necrosis factor (TNF) inhibitors

Six placebo RCTs of TNF inhibition in AS were found which examined pain and/or function as separate outcomes. For spinal pain, etanercept (pooled ES 2.25, 95% CI 1.92 to 2.59)<sup>133–136</sup> and infliximab (ES 0.90, 95% CI 0.66 to 1.14)<sup>137 138</sup> both gave large improvements, with a pooled ES for spinal pain of 1.36 (95% CI 1.16 to 1.55). Three of these studies reported a moderate effect of treatment on peripheral joint pain,<sup>133 135 137</sup> with a pooled ES of 0.61 (95% CI 0.27 to 0.95). Significant effects (pooled ES 1.39, 95% CI 1.20 to 1.57) were also seen for improvement in function, as measured by the BASFI in all studies: for etanercept, the pooled ES was 2.11 (95% CI 1.81 to 2.41) and for infliximab ES was 0.93 (95% CI 0.69 to 1.17). The NNT to achieve an ASAS20 response with infliximab was 2.3 (95% CI 1.9 to 3.0), and for etanercept was 2.7 (95% CI 2.2 to 3.4). Pooling results for both etanercept and infliximab, the NNT with TNF blockers to achieve an ASAS20 response in patients with active disease was 2.6 (95% CI 2.2 to 3.0). To date there is only one AS open trial of adalimumab, the most recent TNF antagonist to become available for treatment in rheumatic diseases, but preliminary data show significant improvements in pain and function.<sup>139</sup>

TNF blocker related toxicity is an important consideration. RCTs reflect some of the well recognised adverse effects of

treatment, including a high incidence of injection site reactions with subcutaneous etanercept (pooled RR from trials in rheumatoid arthritis and AS was calculated at 3.12, 95% CI 2.50 to 3.90 compared with placebo) and development of antinuclear antibodies with intravenous infliximab (pooled RR 2.38, 95% CI 1.61 to 3.53). Other expected toxicities did not reach statistical significance in the RCTs pooled, but the nature of patient selection in such trials and the relatively low incidence of more serious adverse events make it difficult to extrapolate these results to everyday clinical practice. It is important to remember that treatment has been associated with increased risk of infection, both of common upper respiratory tract infections and of opportunistic infections<sup>140–141</sup>—in particular, tuberculosis.<sup>142–143</sup> Screening for *Mycobacterium tuberculosis* has been shown to decrease the incidence of tuberculosis disease associated with TNF blockers,<sup>144</sup> and is now a standard prerequisite for TNF blocker treatment. Demyelinating disease,<sup>145</sup> lupus-like syndromes,<sup>146–148</sup> and worsening of pre-existent congestive heart failure<sup>149–151</sup> have also been reported in case series, although precise incidences are not known.

### Interleukin 1 inhibitors

The only other non-TNF biological modifier to be studied in AS to date is the interleukin 1 inhibitor anakinra, again only in open label trials.<sup>152–153</sup> Results are not consistent, with one study<sup>152</sup> showing a significant improvement in pain ( $p = 0.04$ ) and function ( $p = 0.02$ ) and the second,<sup>153</sup> failing to find any significant improvements with treatment.

### Radiation

#### Local irradiation

Observational studies<sup>154–156</sup> and one RCT<sup>157</sup> were retrieved showing that local irradiation to the spine and sacroiliac joints in patients with AS is effective for pain relief for up to 12 months (level Ib evidence). Physical function was not assessed. There is a large body of evidence for the carcinogenicity of this treatment,<sup>158–161</sup> particularly for leukaemia (RR 2.74, 95% CI 2.10 to 3.53) and other cancers of irradiated sites (RR 1.26, 95% CI 1.19 to 1.32) compared with patients with AS not treated with  $x$  rays.<sup>162–163</sup>

#### Intravenous radium-224 chloride

Intravenous treatment with the radioactive isotope radium chloride (<sup>224</sup>Ra) is largely of historical interest, and not available today for the treatment of AS in most countries. It was used at high doses in the 1940s and 1950s for the treatment of various bone and joint diseases, including tuberculosis and AS. Such high doses have since been abandoned owing to unacceptable toxicity,<sup>164</sup> but lower doses are currently in use since the reintroduction of intravenous <sup>224</sup>Ra for AS in Germany in 2000.<sup>165</sup> <sup>224</sup>Ra has been shown to be effective for pain and spinal stiffness in AS in observational studies—most uncontrolled (best evidence level Ib).<sup>166–172</sup> There has been no formal assessment of the effect of <sup>224</sup>Ra on physical function. Owing to variable study reporting and different study outcome measures it was not possible to calculate pooled ES, but “response” rates reported by patients range from 40% to 90%. Toxicity remains a problem with lower dose treatment, with a significantly higher incidence of myeloid leukaemia and bone malignancies in treated patients compared with the normal population.<sup>173</sup>

### Surgical interventions

#### Total hip arthroplasty

There were numerous prospective cohort studies of total hip replacement (THR) in AS, but RCTs were limited to comparisons between surgical techniques and therefore

beyond the scope of this review. The largest case series to date reviewed 340 hips with a mean follow up of 14 years, and showed that 83% of patients reported good to excellent pain relief, and 52% good to excellent functional improvement after the procedure.<sup>174</sup> Patients undergoing surgery were younger (mean age 40 years) than comparative cohorts undergoing THR for other indications such as osteoarthritis.<sup>175</sup> Results from large databases of THR show that age and sex, independent of joint disease, predict revision.<sup>176</sup> However, revision rates in the study group<sup>174</sup> were not unduly high, with a 90% survival probability at 10 years, and 65% at 20 years. Joint revisions were also seen to perform well, with a 20 year survival of 61%. Most failures occurred within the first 7 years, and were most often due to prosthesis loosening. A high incidence of heterotopic bone formation and re-ankylosis after THR has been reported in early studies of THR in AS<sup>177–178</sup>; however, rates are much lower in contemporary studies.<sup>179–182</sup>

#### Spinal surgery

Surgery for fixed kyphotic deformity causing major disability can give excellent functional results by restoring balance and horizontal vision and relieving intra-abdominal pressure. It is not clear which of the three commonly performed procedures, opening wedge osteotomy, polysegmental wedge osteotomy, and closing wedge osteotomy, gives the best results for any specific indication.<sup>183</sup> Correction ranges from 10° to 60° in different series.<sup>184–194</sup> Rates of complications vary markedly between studies, opening wedge osteotomy being the only procedure reported to be associated with permanent neurological complications.<sup>184</sup> Instrumentation failure has been commonly reported, in up to 33% of cases in one series.<sup>187</sup> Surgery for other indications in AS is uncommon, and large series are lacking in the literature. A case review of operative compared with non-operative treatment for spinal fracture with neurological deficit in AS did not show any differences in outcome between the groups. However, the length of hospital stay was shorter in the non-operative group and hence costs were lower in that group.<sup>195</sup> Operative results in small case series have shown high mortality (16–29%).<sup>196–197</sup>

### DISCUSSION

This systematic literature review identified available treatments effective for symptomatic control of spinal pain and physical function in AS. Both NSAIDs and coxibs have large effects on spinal pain and moderate benefit for physical function. TNF inhibitors are effective in patients with active disease, with large benefits seen in pain and function. Results with other traditional DMARDs are less encouraging, without convincing evidence of an effect on the spinal symptoms of AS, although there may be a role for sulfasalazine or methotrexate in the treatment of peripheral joint disease. Total hip arthroplasty is valuable in patients with significant hip disease, and spinal surgery can be useful in selected patients. Non-pharmacological treatments are also supported by current research evidence for maintaining function in patients with AS.

It is less clear if any treatments modify disease progression; this literature review was designed to answer the question “what interventions have an effect on pain or function in AS” and as such was not directed at the effect of treatment on structural changes. Continuing studies of TNF inhibitors in AS over 2 and 3 years are now beginning to answer this important question.

As with any literature review, this study is limited by the unavoidable publication bias associated with clinical trials, where trials with positive results are more frequently published than negative studies. This may have resulted in

an overestimation of true clinical efficacy. The variable quality of the reporting of clinical trials before the CONSORT statement for standardisation of the reporting of clinical trials<sup>198 199</sup> was published also contributes potential bias—for example, when specific information could not be retrieved from the paper and the authors could not be contacted.

This review is a comprehensive summary of the current “best evidence” available for therapeutic interventions, both pharmacological and non-pharmacological, for the management of AS, and formed the basis for the development of the ASAS/EULAR recommendations for management of AS.<sup>1</sup>

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## APPENDIX 1 SEARCH STRATEGY FOR ANKYLOSING SPONDYLITIS

Database: Ovid MEDLINE(R) <1966 to December Week 4 2004>

Search Strategy:

- 1 exp ANKYLOSING SPONDYLITIS/ (7445)
- 2 spondyloarthr\$.mp. (1620)
- 3 ankylosi\$.mp. (8424)
- 4 syndesmophyt\$.mp. (113)
- 5 1 or 2 or 3 or 4 (12302)
- 6 limit 5 to human (2433)

## APPENDIX 2 SEARCH STRATEGY FOR TYPES OF EVIDENCE

Database: Ovid MEDLINE(R) <1966 to December Week 4 2004>

Search Strategy:

- 1 systematic review\$.mp. (6835)
- 2 exp meta-analysis/ (5713)
- 3 meta-analysis\$.mp. [mp = title, abstract, name of substance, mesh subject heading] (14204)
- 4 exp systematic review/ (0)
- 5 1 or 2 or 3 or 4 (19490)
- 6 limit 5 to human (18685)
- 7 cohort stud\$.mp. or exp Cohort Studies/ (520224)
- 8 case control stud\$.mp. or exp Case-Control Studies/ (277571)
- 9 cross sectional stud\$.mp. or exp Cross sectional Studies/ (60617)
- 10 risk ratio\$.mp. or exp Odds Ratio/ (25051)
- 11 relative risk\$.mp. (27401)

- 12 7 or 8 or 9 or 10 or 11 (811260)
- 13 limit 12 to human (796187)
- 14 exp “Costs and Cost Analysis”/ or exp Cost-Benefit Analysis/ or economic evaluation.mp. or exp Economics, Medical/ (121450)
- 15 cost effectiveness analys\$.mp. (2713)
- 16 cost utility analys\$.mp. (473)
- 17 cost minimisation analys\$.mp. (170)
- 18 cost benefit analys\$.mp. (34956)
- 19 cost analys\$.mp. (2319)
- 20 14 or 15 or 16 or 17 or 18 or 19 (122698)
- 21 limit 20 to human (87101)
- 22 exp Randomised Controlled Trials/ or randomised controlled trial\$.mp.
- or exp Clinical Trials/ or exp Random Allocation/ (208880)
- 23 exp Double-Blind Method/ or double blind.mp. or exp Placebos/ (111321)
- 24 single blind.mp. or exp Single-Blind Method/ (11613)
- 25 Comparative Study/ (1188913)
- 26 prospective stud\$.mp. or exp Prospective Studies/ (200630)
- 27 follow up stud\$.mp. or exp Follow-Up Studies/ (301986)
- 28 22 or 23 or 24 or 25 or 26 or 27 (1769477)
- 29 limit 28 to human (1342425)
- 30 6 or 13 or 21 or 29 (1697116)

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