REVIEW ARTICLE

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Pharmacological Treatment of Ankylosing Spondylitis

A Systematic Review

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Abstract

The purpose of this study was to review the evidence regarding the efficacy and safety of pharmacological therapies currently available for the treatment of ankylosing spondylitis (AS).

A literature search using MEDLINE from 1966 through to April 2005 and a hand search of abstracts from the American College of Rheumatology (ACR) meetings for 2001 through to 2004 were performed. References of articles retrieved were also searched.

The MEDLINE search yielded 570 citations and 157 abstracts from ACR were identified. Eighty-four studies were randomised controlled trials (RCTs); 53 fulfilled the inclusion criteria (pharmacological treatment of AS and RCT) and were included in this review. Statistical pooling of data was not performed because of the disparate outcome measures used. Eight RCTs found nonselective NSAIDs and two RCTs found cyclo-oxygenase (COX)-2-selective NSAIDs to be superior to placebo for relief of pain and improvement in physical function. Twenty-nine RCTs showed comparable efficacy and safety between nonselective

NSAIDs. One RCT showed no difference between methylprednisolone 1g and 375mg. Seven RCTs assessing the efficacy of sulfasalazine (sulphasalazine) and two RCTs of methotrexate provided contradictory evidence as to their benefit for treatment of AS. One RCT showed intravenous pamidronate 60mg to be more effective than 10mg intravenously for the treatment of axial pain. All six RCTs of anti-tumour necrosis factor (TNF)-α agents demonstrated superiority to placebo for the treatment of axial and peripheral symptoms.

Nonselective as well as COX-2-selective NSAIDs can be used for pain control in patients with AS. Other proven treatment options include sulfasalazine for the treatment of peripheral joint symptoms, while limited evidence supports the use of pamidronate or methotrexate, which require further studies. Anti-TNFα agents have been found very effective for the treatment of both peripheral and axial symptoms in patients with AS, but their use is limited by cost and uncertainty over long-term efficacy and safety.

Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the sacroiliac joint and spine. AS typically presents before the age of 40 years with an insidious onset of inflammatory low back pain.[1] Associated comorbidities include asymmetric peripheral arthritis, enthesopathy, inflammatory eye disease and a variety of skin disorders. The prevalence of AS varies among populations, ranging from 0.1% in African and Inuit populations to between 0.3% and 1.4% in North Americans and Europeans.[2-6] Prevalence also varies by sex, with a male to female ratio of 3.5 : 1,[3] and by HLA-B27 status. Consistent with the genetic predisposition, persons expressing this phenotype have a 20-fold higher risk for developing a spondyloarthropathy compared with those who are HLA-B27 negative;[4] the pathophysiology for this association is currently unknown.

Progressive structural damage occurs if AS is left untreated. In a study of patients followed for 4 years, 55% had progressive damage as monitored by cervical and lumbar radiographs.[7] The early onset of AS and its progressive joint damage impose a significant burden on patients and payers. Using information from a national German database, the annual direct and indirect costs for males with AS were calculated at $US9151/year (year 2000 value), slightly lower than the amount ($US9971) for males with rheumatoid arthritis (RA).[8] In this study, the proportion of patients taking disease-related early retirement and the costs due to sick leave and work disability were similar for AS and RA, with indirect costs twice as high as direct costs. In a US study, researchers found that indirect costs of AS, which were mainly due to lost work productivity, were three times higher than the direct costs.[9] In a mail survey of 2384 patients with AS who were members of the Spondylitis Association of America, 15% reported work-related disability attributable to AS. Duration of disease was the most important predictor of work-related disability.[10]

Early diagnosis and aggressive treatment should be encouraged because of the considerable burden of illness, both for the patient and for society. The objective of this study was to perform a literature review of the evidence regarding the efficacy and safety of pharmacological treatment options currently available for AS.

1. Literature Review

1.1 Methods

A review of the literature was performed by searching the keywords 'ankylosing' and 'drug therapy' as minor and major subject headings in MEDLINE from 1966 through to April 2005. In addition, abstracts from the American College of Rheumatology (ACR) meetings for 2001, 2002, 2003 and 2004 were searched by hand. The inclusion criteria

Table I. Randomised controlled trials (RCTs) identified for evaluation of pharmacological treatment of ankylosing spondylitis by therapeutic class

Therapeutic agent	RCTs retrieved (n = 75)	RCTs excluded (n = 24)	RCTs with usable data (n = 51)
NSAIDs	50	16	34 (table III)
Corticosteroids	3	2	1 (table IV)
Sulfasalazine	10	3	7 (table V)
Pamidronate	3	2	1 (table VI)
Anti-TNFα	12	6	6 (table VII)
Methotrexate	4	2	2 (table VIII)
Amitriptyline	1	0	1 (table VIII)
Penicillamine	1	0	1 (table VIII)
Total	**84**	**31**	**53**

TNF = tumour necrosis factor.

for the initial search were pharmacological treatment of AS and randomised controlled trial (RCT). The exclusion criteria included: open studies; case reports; articles not in the English, French or Spanish language; and studies in which the treatment group was not limited to AS (table I). A detailed description of the search strategy is included in table II.

Abstracts and full articles that met the inclusion/exclusion criteria were retrieved. The bibliographies of these articles were also reviewed for additional references. Methodological quality of the articles/abstracts was assessed using Jadad et al.'s validated instrument for RCTs,[11] which is based on randomisation, blinding of treatment allocation and description of withdrawals. The scores can range from zero to five. Studies included in this review were RCTs evaluating pharmacological therapies for the symptomatic treatment of AS that scored at least 3 on the Jadad scale.

Data abstraction of outcomes reported in the studies was performed using a systematic approach. As endpoints in the trials varied, it was decided to focus on the most frequently reported endpoints (i.e. Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Bath Ankylosing Spondylitis Functional Index [BASFI], Assessment in Ankylosing Spondylitis [ASAS] criteria, and pain scores). Other outcomes (including spinal mobility measures such as Schober's test, chest expansion and finger-to-toe distance) and laboratory measures (such as C-reactive protein) have not been shown to be responsive in short-term trials[12] and, therefore, are not reported here.

The BASDAI and BASFI are validated instruments that are based on a composite score of clinical symptoms associated with AS.[13-15] The definition of what constitutes a minimally clinically important difference, as measured by the BASDAI, varies among studies from improvement of at least 20% to 50% or greater.[16-18] More recently, the ASAS working group has suggested that the definition of clinical response should include both a relative improvement of ≥20% and an absolute improvement of ≥10 units (on a scale of 0–100) in at least three of four domains: (i) patient global assessment; (ii) pain; (iii) function; and (iv) inflammation.[12] Furthermore, there should be no deterioration in the potential remaining domain, where deterioration is defined as change for the worse of ≥20% and net worsening of ≥10 units (on a scale of 0–100).

In addition to the clinical effectiveness of AS therapies, the safety of the agents was also reviewed. The focus was on serious adverse events only, as reported in the RCTs included in this review. Statistical pooling of data in a meta-analysis was not considered appropriate because of disparate outcome measures used among trials.

1.2 Assessment of Potentially Relevant Articles

The literature search generated 570 citations. In addition, 157 abstracts containing the keyword 'an-

kylosing spondylitis' were identified. Of these, 84 studies, including five abstracts, met the inclusion criteria for this review article, as per table II. Upon removing duplicates and those that did not include relevant endpoints or scored <3 on the Jadad scale, 53 articles remained (table I). Results of the review are reported by therapeutic class. Table I illustrates the therapeutic agents studied in the 53 RCTs included in this review.

Table II. Literature search schematic showing how randomised controlled trials of drug therapy for ankylosing spondylitis were selected for review

Search strategy
"Ankylosing" and "drug therapy" as minor and major subject headings
Search limited to
articles in English, French or Spanish
study of humans
case report or comparative study
classical-article
clinical-conference
clinical-trial, clinical-trial-phase-I, clinical-trial-phase-II, clinical-trial-phase-III, clinical-trial-phase-IV
congresses
controlled-clinical-trial
evaluation-studies
guideline
journal-article
meta-analysis
multicenter-study
practice-guideline
randomised-controlled-trial
review or review-academic
review-literature
review-multicase
review-reported-cases
review-tutorial
scientific-integrity-review
technical-report
validation-studies
Articles excluded
case reports
procedures or drug applications
drug reviews for various indications
studies in which the treatment groups was not limited to ankylosing spondylitis

2. Results by Therapeutic Class

2.1 NSAIDs

Fifty articles evaluating NSAID therapy were retrieved. Of these, 16 were excluded because: in four studies,[19-22] patients were not randomised; in three,[23-25] patients were not blinded to treatment allocation; in one,[26] results of patients with AS and osteoarthritis were combined; in one,[27] results were reported in an article already included; one[28] was an abstract of a published full-length paper; and the final six studies scored <3 on the quality-rating scale.[29-34] The remaining 34 studies are summarised in table III.

Eight articles compared traditional nonselective NSAIDs and placebo in the treatment of AS.[37,40,42,43,53,60,66,68] All demonstrated nonselective NSAIDs to be superior to placebo for the relief of spine pain, global pain and improvement in disease activity. Twenty-nine RCTs (including five of the aforementioned) described comparisons between different nonselective NSAIDs. Results of these studies found different nonselective NSAIDs to be comparable in efficacy and safety in the treatment of AS.[37-41,44-65,67,68] Serious adverse events were uncommon and were predominantly gastrointestinal (GI) events, including ulcers.

The cyclo-oxygenase (COX)-2-selective inhibitors (coxibs) have also been shown to be effective therapies for AS.[35,36] In a 6-week trial comparing celecoxib 100mg twice daily with ketoprofen 100mg twice daily or placebo in 246 patients, both active treatments were more effective than placebo in improving pain and function.[36] There were no significant differences between active treatments.

The COX-2-selective inhibitor etoricoxib was compared at doses of 90 and 120mg once daily with naproxen 500mg twice daily and placebo in a study of 387 patients with AS.[35] The results showed superior efficacy of both etoricoxib doses compared with placebo for the treatment of spine pain, patient global assessment and BASFI after 6 weeks of therapy. Additionally, both etoricoxib doses were superior to naproxen for improvement in spine pain and BASFI at 46 weeks.

Table III. Summary of randomised controlled trials (RCTs) of NSAIDs for the treatment of ankylosing spondylitis

Study (year)	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints[b]	p-Value
van der Heijde et al.[35] (2005)	5	6	301/86	Etoricoxib (E_1) 90mg od Etoricoxib (E_2) 120mg od Naproxen (N) 500mg bid Placebo (P)	43 (12) 43 (12) 45 (11) 44 (12)	NA	Spinal pain (100mm VAS) BASFI	<0.001 (E_1, E_2, N vs P) <0.05 (E_1, E_2 vs N) <0.001 (E_1, E_2, N vs P)
van der Heijde et al.[35] (2005)	5	46	374[c]	Etoricoxib (E_1) 90mg od Etoricoxib (E_2) 120mg od Naproxen (N) 500mg bid	NA	NA	Spinal pain (100mm VAS) BASFI	<0.05 (E_1 vs N) <0.01 (E_2 vs N) <0.05 (E_1 vs N) <0.05 (E_2 vs N)
Dougados et al.[36] (2001)	4	6	208/38	Celecoxib (C) 100mg bid Ketoprofen (K) 100mg bid Placebo (P)	38 (11) 38 (11) 40 (11)	11 (9) 11 (10) 11 (9)	Global pain intensity (100mm VAS) BASFI	0.0068 (C vs P) NS (K vs P) NS (C vs K) 0.0006 (C vs P) 0.0436 (K vs P) NS (C vs K)
Dougados et al.[37] (1999)	3	6	370/103	Piroxicam (PIR) 20mg od Meloxicam (M1) 15mg od Meloxicam (M2) 22.5mg od Placebo (P)	44 (13) 44 (12) 42 (12) 40 (12)	12 (11) 13 (9) 12 (10) 12 (9)	50% improvement in pain (100mm VAS)	0.0167 (PIR vs P) 0.0167 (M1 vs P) 0.0167 (M2 vs P) NS (PRI vs M1) NS (PRI vs M2)
Batlle-Gualda et al.[38] (1996)	5	12	172/138	Aceclofenac 200mg od Indometacin 100mg od	38 (8) 39 (8)	8 (7) 7 (8)	Pain (100mm VAS)	NS
Villa Alcazar et al.[39] (1996)	4	4	218/55	Aceclofenac 100mg bid Tenoxicam 20mg od	6 (6) 5 (5)	37 (8) 37 (8)	Pain (100mm VAS)	NS
Dougados et al.[40] (1994)	5	2	195/90	Ximoprofen (X) 30mg od 20mg od 10mg od 5mg od Placebo	40 (12) 40 (13) 40 (10) 40 (10) 40 (11)	10 (8) 8 (8) 8 (7) 10 (8) 10 (8)	Pain (100mm VAS) >50% improvement vs baseline	0.0001 (all X vs P)
Carcassi et al.[41] (1990)	4	12	119[c]	Indometacin 25–50mg tid Pirazolac 300–600mg bid	40 (20–62) 37 (18–72)	10.5 (1–50) 9.9 (0–40)	Night pain Spinal pain (100mm VAS)	NS
Dougados et al.[42] (1989)	4	2	33/3	Ximoprofen (X) 15mg bid Placebo (P) bid	36 (20–65)	9 (1–32)	Pain (100mm VAS)	0.01 (X vs P)
Dougados et al.[43] (1987)	4	2	31/7	Piroxicam (PIR) 200mg od Placebo (P)	35 (8) 38 (12)	9 (6) 8 (6)	Pain (100mm VAS)	0.001 (PIR vs P)
Bird et al.[44] (1986)	5	4	25/5	Tenoxicam 20mg od Piroxicam 20mg od	38 (NA) 46 (NA)	NA	Spinal pain upon rising in AM (0–5) Night pain (0-5)	NS

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Table III. Contd

Study (year)	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints[b]	p-Value
Calabro[45] (1986)	3	15	284[c]	Diclofenac 25mg tid (max. 125 mg/day) Indometacin 25mg tid (max. 125 mg/day)	NA (19–67)	NA	Spinal pain (0–4) Nocturnal pain (0–3)	NS
Doury and Roux[46] (1986)	4	4	16/3	Isoxicam 200mg od Ketoprofen 100mg tid	43 (NA)	11 (NA)	Subjective pain (100mm VAS)	NS
Franssen et al.[47] (1986)	4	12	38/0	Diflunisal 500mg bid Phenylbutazone 200mg od	NA (18–55)	NA	Spinal pain (0–4) Lumbar sacroiliac pain (0–4)	NS
Lomen et al.[48] (1986)	4	26	77/8	Flurbiprofen 200–300mg od Phenylbutazone 300–500mg qid	NA	6.2 (NA)	Night pain (0–3) Spinal pain (0–4) Rest pain (0–4) Motion pain (0–6)	NS
Lomen et al.[49] (1986)	3	26	54/7	Flurbiprofen 200mg od Indometacin 100mg od	NA (18–65)	NA (0–30)	Night pain (0–3) Spinal pain (0–4) Rest pain (0–4) Motion pain (0–6)	NS
Khan[50] (1985)	4	13	187/37	Diclofenac 75–125mg od Indometacin 75–125mg od	39 (19–64) 38 (19–64)	NA	Spinal pain (0–3)	NS
Armstrong et al.[51] (1984)	5	8	18/1	Indoprofen 200mg qid Indometacin 25mg qid	44 (24–60)	14 (NA)	Pain score (100mm VAS)	NS
Tannenbaum et al.[52] (1984)	4	12	41/14	Piroxicam 10–20mg od Indometacin 25mg tid (max. 125 mg/day)	36 (1) 34 (2)	9 (1) 10 (2)	Pain (17-point VAS)	NS
Jajic et al.[53] (1982)	3	6	104[c]	Pirprofene 100mg od Indometacin 125mg od Placebo	35 (NA)	NA	Pain at rest (0–3) Pain with movement (0–4)	NS
Romberg[54] (1982)	4	10	67/20	Piroxicam (P) 20mg od Indometacin (I) 25mg tid	40 (NA)	NA	Back pain (10cm VAS) Peripheral joint pain at rest (10cm VAS)	<0.01 (P vs I)
Sydnes[55] (1981)	4	4	67/20	Piroxicam 20mg od Indometacin 25mg tid	40 (18–70)	NA	Back pain (10cm VAS)	NS
Bird et al.[56] (1980)	4	4	20[c]	Indometacin (I) 25mg tid Benoxaprofen (B) 600mg od	NA	NA	Spinal pain (VAS) Night pain (VAS)	NS 0.01 (I vs B)
Burry and Siebers[57] (1980)	4	4	26/3	Flurbiprofen 200mg od Naproxen 750mg od	NA	NA	Pain (0–5)	NS

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Table III. Contd

Study (year)	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints[b]	p-Value
Nahir and Scharf[58] (1980)	4	4	2/60	Diclofenac (D) 50mg tid Sulindac (S) 200mg bid	37 (NA) 37 (NA)	NA	Pain (100mm VAS) Spinal pain (0–4)	0.048 (D vs S) NS
Rejholec et al.[59] (1980)	5	24	43/7	Tolfenamic acid 200mg tid Indometacin 25mg tid	39 (NA) 36 (NA)	14 (NA) 10 (NA)	Pain index (0–3)	NS
Shipley et al.[60] (1980)	4	6	18/1	Indometacin (I) 50mg tid Fenoprofen (F) 600mg tid Placebo (P)	38 (21–53)	NA	Spinal pain (VAS) [logarithmic mean]	NS (I vs F) <0.01 (I vs P) <0.05 (F vs P)
Wordsworth et al.[61] (1980)	4	4	22/6	Fenoprofen (F) 600mg tid Phenylbutazone (P) 100mg tid	NA	15 (NA)	Overall pain (10cm VAS) Spinal pain (10cm VAS)	NA
Ansell et al.[62] (1978)	4	8	23/2	Naproxen 250mg morning + 500mg night Phenylbutazone 100mg tid	NA (25–69)	NA	Morning pain (0–3)	NS
Mena and Willkens[63] (1977)	4	6	21/6	Flurbiprofen 150–200mg od Phenylbutazone 300–400mg od	NA	NA	Day pain (0–4) Night Pain (0–4)	NS
Jessop[64] (1976)	4	8	17/3	Ketoprofen 50mg qid Phenylbutazone 75mg qid	40 (NA)	17 (NA)	Severity of pain (0–4)	NA
Treadwell and Tweed[65] (1975)	4	8	13/1	Ketoprofen 25mg qid Phenylbutazone 50mg qid	36 (23–55)	NA (2–30)	Pain (0–2)	NA
Calcraft et al.[66] (1974)	4	4	17/11	Azapropazone 900mg od Placebo	NA (28–69)	NA	Back pain (0–3)	NS
Calin and Grahame[67] (1974)	4	4	32/5	Flurbiprofen 150mg od Phenylbutazone 300mg od	42 (18–69)	11 (1–29)	Day pain (1–5) Night pain (1–5)	NS
Sturrock and Hart[68] (1974)	4	6	21/3	Indomethacin (I) 25mg tid Flurbiprofen (F) 50mg tid Placebo (P)	43 (NA)	17 (NA)	Pain (10cm VAS)	<0.05 (F vs I) <0.01 (F vs P) <0.05 (I vs P)

a Quality of articles was assessed using the validated instrument of Jadad et al.[11] with a scale of 0–5.

b RCTs with the following outcomes are reported: BASDAI, BASFI, ASAS criteria and pain scores.

c Number of female and male patients not provided.

ASAS = Assessment in Ankylosing Spondylitis: **BASDAI** = Bath Ankylosing Spondylitis Disease Activity Index; **BASFI** = Bath Ankylosing Spondylitis Functional Index; **bid** = twice daily; **max.** = maximum; **NA** = data not provided; **NS** = not significant; **qid** = four times daily; **od** = once daily; **SD** = standard deviation; **tid** = three times daily; **VAS** = visual analogue scale.

Table IV. Summary of single randomised controlled trial of intravenous corticosteroids for the treatment of ankylosing spondylitis included based on quality score and outcomes measured

Study (year)	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/ female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints	p-Value
Peters and Ejstrup[70] (1992)	4	24	13/4	Methylprednisolone 1g IV Methylprednisolone 375mg IV	41 (31–55) 39 (25–61)	10.5 (1–20) 7 (1–22)	Pain (VAS)	NS

a Quality of articles was assessed using the validated instrument of Jadad et al.[11] with a scale of 0–5.

IV = intravenous; **NS** = not significant; **SD** = standard deviation; **VAS** = visual analogue scale.

There is limited evidence that treatment with NSAIDs has a positive effect on disease progression. However, a recent abstract reported preliminary results from a 2-year study comparing continuous versus intermittent use of NSAIDs, suggesting a decrease in radiographic progression only in patients receiving continuous treatment.[69]

2.2 Corticosteroids

Three articles describing the use of corticosteroids were retrieved; only one was included in this review (table IV).[70] Two studies evaluated the use of intra-articular sacroiliac joint injection, which provided pain relief in this region at 2 and 6 months compared with placebo.[71,72] These two studies were excluded because they evaluated patients with spondyloarthropathy and not just AS, as per our protocol.

The one study included, which was an RCT comparing intravenous methylprednisolone 1g versus 375mg,[70] found no differences between treatment groups. No published placebo-controlled trials evaluating oral or intravenous corticosteroid use for the treatment of AS were identified.

2.3 Sulfasalazine

Ten articles reporting evaluations of sulfasalazine (sulphasalazine) for the treatment of AS were identified.[73-82] Three of these were excluded because one was a meta-analysis;[78] patients were not randomised in the second study;[75] and the third[73] was a re-analysis of a study that was already included. The remaining seven RCTs (table V) provided inconclusive evidence concerning the efficacy of sulfasalazine in AS.

In the largest of these studies of sulfasalazine, 264 patients were assessed over a 36-month period.[74] No difference in the primary outcome measure was found between patients treated with sulfasalazine and those treated with placebo.[74] Four other studies also found no difference between sulfasalazine and placebo regarding pain control.[77,79,80,82]

Four studies reported improvements in some of the endpoints measured in patients treated with sulfasalazine;[76,80-82] however, the outcomes assessed differed among the studies. Additionally, these studies analysed multiple endpoints (10–16) without correcting for multiple statistical tests, potentially resulting in an increased chance for a type I statistical error.

Only one serious event, an erythematous raised purpuric rash associated with nausea, anorexia and insomnia, was reported in a sulfasalazine group in one of the seven studies.[74]

2.4 Pamidronate

Bisphosphonates have been shown to induce osteoclast apoptosis and to be effective in animal models of established arthritis.[83-85] The literature search identified three studies in which pamidronate was tested for the treatment of symptomatic AS.[86-88] Two studies were excluded because one was an abstract[87] of an already included paper and the other[88] was a substudy of another reported study that is summarised in table VI.[86]

Table V. Summary of randomised controlled trials (RCTs) of sulfasalazine for the treatment of ankylosing spondylitis

Study (year)	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints[b]	p-Value
Clegg et al.[74] (1996)	4	36	191/73	Sulfasalazine 2g Placebo	44 (NA) 45 (14)	18 (NA) 19 (12)	Composite index[c]	NS
Dougados et al.[81] (1986)	5	24	46/14	Sulfasalazine (S) 2g Placebo (P)	39 (NA) 37 (NA)	10 (NA) 10 (NA)	Pain (100mm VAS)	<0.005 (S vs P)
Feltelius and Hallgren[82] (1986)	3	12	28/9	Sulfasalazine 3 g/day Placebo	41 (25–57) 37 (20)	12 (2–30) 10 (2–20)	Pain severity (100mm VAS) Sacroiliac pain (100mm VAS) Number of painful joints	NS
Taylor et al.[76] (1991)	3	48	40[d]	Sulfasalazine (S) Placebo (P)	35 (2) 39 (2)	3 (1) 3 (2)	Pain (10cm VAS)	<0.05 (S vs P)
Corkill et al.[77] (1990)	5	48	54/8	Sulfasalazine 2g Placebo	37 (9) 28 (11)	12 (8) 16 (11)	Spinal pain (VAS) Peripheral joint pain (VAS)	NS
Davis et al.[79] (1989)	4	12	25/3	Sulfasalazine 2g Placebo	35 (23–49) 40 (21–57)	8.6 (1–30) 8.4 (1–25)	Pain (10cm VAS)	NS
Nissila et al.[80] (1988)	4	26	67/18	Sulfasalazine 3g Placebo	37 (9) 39 (8)	4 (4) 5 (7)	Severity of spinal pain (VAS)	NS

a Quality of articles was assessed using the validated instrument of Jadad et al.[11] with a scale of 0–5.

b RCTs with the following outcomes are reported: BASDAI, BASFI, ASAS criteria and pain scores.

c Treatment response defined as improvement in two of four measures (patient and physician assessments, duration of morning stiffness and severity of back pain).

d Number of female and male patients not provided.

ASAS = Assessment in Ankylosing Spondylitis: **BASDAI** = Bath Ankylosing Spondylitis Disease Activity Index; **BASFI** = Bath Ankylosing Spondylitis Functional Index; **NA** = data not provided; **NS** = not significant; **SD** = standard deviation; **VAS** = visual analogue scale.

Table VI. Summary of single randomised controlled trial of pamidronate for the treatment of ankylosing spondylitis included based on quality score and outcomes measure

Study (year)	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints	p-Value
Maksymowych et al.[86] (2002)	5	24	67/17	Pamidronate 60mg IV	38.8 (24–65)	14 (2–33)	BASDAI reduction >25%	0.004[b]
				Pamidronate 10mg IV	40.3 (25–65)	16 (1–44)	BASDAI reduction >50%	0.027[b]
							BASDAI reduction >70%	NS

a Quality of articles was assessed using the validated instrument of Jadad et al.[11] with a scale of 0–5.

b Pamidronate 60mg was superior to pamidronate 10mg.

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; **IV** = intravenous; **SD** = standard deviation.

In the included dose-response study, 84 patients with NSAID-refractory AS were treated with either 60mg or 10mg of intravenous pamidronate.[86] The control group received pamidronate 10mg, rather than placebo, because the first dose of pamidronate frequently causes arthralgias, and the lack of this adverse effect could have revealed treatment allocation. The minimum dose of pamidronate shown to provoke such post-infusion arthralgias is 10mg.[89] At 6 months, significant reductions in BASDAI and BASFI were apparent in the 60mg group compared with the 10mg group. Serious adverse events, including transient arthralgias/myalgias after the first infusion, were similar in both groups.

2.5 Anti-Tumour Necrosis Factor-α Agents

The rationale for treating AS with a tumour necrosis factor (TNF)-α-blocking agent is based on the observation that large amounts of TNFα are expressed at the site of inflammation in patients with this disease.[90] The literature search identified 12 references describing studies of the anti-TNFα agents infliximab and etanercept for treatment of AS.[16-18,91-99] Six of the 12 studies were excluded because one was a substudy of a published RCT[94] and five were abstracts of studies also available as full-length papers.[95-99] The remaining six studies are summarised in table VII.

Infliximab, a chimeric murine/human monoclonal anti-TNFα antibody, was compared at a dose of 5 mg/kg with placebo in 69 patients with AS in a 12-week study.[18] At week 12, patients receiving infliximab showed a significant regression of disease activity compared with placebo, as measured by the proportion of patients with a ≥50% improvement on BASDAI. Another study evaluated infliximab at the same dose over a 24-week period. This study also demonstrated the superior efficacy of infliximab over placebo in the ASAS 20, BASDAI and BASFI.[91] The former study reported three serious adverse events, one each in three patients treated with infliximab (systemic tuberculosis, allergic pulmonary granulomatosis, and mild leukopenia). The latter study reported seven patients (3.5%) having serious events with the use of infliximab, including one each

Table VII. Summary of randomised controlled trials (RCTs) of anti-tumour necrosis factor (TNF)-α agents for the treatment of ankylosing spondylitis

Study (year)	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints[b]	p-Value
van der Heijde et al.[91] (2005)	5	24	225/54	Infliximab (I) 5 mg/kg IV	40 (32–47)	8 (3–15)	ASAS 20[c]	<0.001 (I vs P)
				Placebo (P)	41 (34–47)	13 (4–18)	BASDI	<0.001 (I vs P)
							BASFI	<0.001 (I vs P)
Calin et al.[92] (2004)	4	12	66/18	Etanercept (E) 25mg 2× weekly	45 (10)	15 (9)	ASAS 20[c]	<0.001 (E vs P)
				Placebo (P)	41 (11)	10 (8)	BASDAI	<0.01 (E vs P)
							BASFI	<0.01 (E vs P)
Davis et al.[93] (2003)	5	24	210/67	Etanercept (E) 25mg 2× weekly	42 (24–70)	10 (0–31)	ASAS 20[c]	<0.0001 (E vs P)
				Placebo (P)	42 (18–65)	11 (0–35)		
Brandt et al.[17] (2003)	4	6	22/8	Etanercept (E) 25mg 2× weekly	40 (9)	15 (8)	BASDAI >50% improvement	0.004 (E vs P)
				Placebo (P)	32 (8)	11 (9)		
Braun et al.[18] (2002)	4	12	45/24	Infliximab (I) 5 mg/kg IV	41 (8)	16 (8)	BASDAI >50% improvement	0.0001 (I vs P)
				Placebo (P)	39 (9)	15 (9)		
Gorman et al.[16] (2002)	4	16	31/9	Etanercept (E) 25mg 2× weekly	38 (10)	15 (10)	ASAS[c]	0.004 (E vs P)
				Placebo (P)	39 (10)	12 (9)		

a Quality of articles was assessed using the validated instrument of Jadad et al.[11] with a scale of 0–5.

b RCTs with the following outcomes are reported: BASDAI, BASFI, ASAS criteria and pain scores.

c ASAS criteria – see text for details.

ASAS = Assessment in Ankylosing Spondylitis: **BASDAI** = Bath Ankylosing Spondylitis Disease Activity Index; **BASFI** = Bath Ankylosing Spondylitis Functional Index; **IV** = intravenous; **SD** = standard deviation.

with dizziness, cholecystitis, arthritis, leukocytosis and pneumonia, inguinal hernia, haemiparesis and abdominal pain, and back pain, fever and ganglioneuroma.

Four RCTs have been reported to date for etanercept, a soluble TNFα-receptor blocker.[16,17,92,93] The duration of treatment was 6–24 weeks in these studies and all four showed superior efficacy of etanercept over placebo. Serious adverse events reported in these trials included one of each of the following: lymphadenopathy, staphylococcal cellulitis after a spider bite, wound infection after a cat bite, bone fracture after a fall, fever associated with injection-site reactions, a flare of ulcerative colitis, intestinal obstruction due to adhesions and acute myocardial infarction. In addition, two bone fractures after trauma were reported.

2.6 Other Therapies

Of the four methotrexate trials reviewed, one was excluded because treatment was not double-blinded[100] and one was an abstract also available as a full-length paper.[101] In the two remaining RCTs, patients received methotrexate 10mg and 7.5mg weekly or placebo for a period of 24 weeks (table VIII).[102,103] The study in which methotrexate was evaluated at 10mg did not demonstrate any difference in BASDAI response between methotrexate and placebo.[102] However, results in the second trial favoured methotrexate, based on good responses measured by a composite index detailed in table VII, but no significant difference in BASDAI between the two groups was found.[103] No serious adverse events were reported in either study.

The use of amitriptyline for treating AS has been evaluated in one RCT (table VIII).[104] In that study, patients remained on the medication(s) they were taking for AS, and the effect of adding amitriptyline or placebo was studied. Results showed that those receiving amitriptyline had significant improvement in BASDAI scores relative to placebo ($p = 0.024$), but no significant changes in pain and BASFI. No serious adverse events were reported in this study.

One RCT studied the use of penicillamine versus placebo for AS (table VII).[105] None of the patients reported any improvement while taking penicillamine.

3. Discussion

This review provides a detailed and precise evaluation of different pharmacological treatment modalities frequently used in daily practice for AS. The review confirms the short-term symptomatic effect of NSAIDs and suggests that new compounds, such as anti-TNFα, may be of interest in NSAID-refractory patients.

According to clinical consensus, NSAIDs are the recommended first-line therapy for the treatment of axial and peripheral pain for patients with AS.[106,107] Since there is no evidence distinguishing among nonselective NSAIDs based on efficacy, other considerations such as tolerability, risk factors, administration schedule and cost should be considered for each patient when NSAIDs are prescribed. To date, etoricoxib and celecoxib are the only COX-2-selective agents that have been studied in AS, and both have been shown to be efficacious for symptomatic treatment of pain and improvement in physical function.

The cardiovascular safety profile of COX-2-selective and nonselective NSAIDs is currently a topic of great interest to scientists, practitioners, patients and regulatory authorities. The US FDA convened a Joint Advisory Committee Meeting in February 2005 to review available cardiovascular safety data, and have since issued results of their analysis and recommendations.[108] It was concluded that the available cardiovascular safety data are best interpreted as being consistent with a class effect of an increased risk of serious cardiovascular events for COX-2-selective and nonselective NSAIDs. Additional long-term controlled clinical trials are necessary to provide more information on these effects.

There is no convincing evidence for oral or intravenous corticosteroid use in the treatment of AS.[70] Intra-articular injections into the sacroiliac joint may be beneficial, although this was not formally evaluated in any studies identified in this review.[71,72] There is some evidence, although limited, that sulfasalazine is beneficial for the treat-

Table VIII. Summary of randomised controlled trials of drugs not included in tables III to VII for the treatment of ankylosing spondylitis

Study	Quality scale[a]	Duration of study (weeks)	No. of patients enrolled (male/female)	Treatment groups	Mean age, years (SD or range)	Mean disease duration, years (SD or range)	Endpoints[b]	p-Value
Gonzalez-Lopez et al.[103] (2004)	5	24	24/11	Methotrexate (M) 7.5mg weekly	NA	NA	Composite Index[c]	0.03 (M vs P)
				Placebo (P)			BASDAI 20	NS
							BASDAI 50	NS
Roychowdhury et al.[102] (2002)	4	24	26/4	Methotrexate 10mg weekly	44 (10)	17 (9)	BASDAI	NS
				Placebo				
Koh et al.[104] (1997)	4	2	78/22	Amitriptyline (A) [mean dose 27.1mg od]	42 (10)	19 (10)	Pain (VAS 0–10)	NS
					46 (10)	22 (12)	BASDAI	0.024 (A vs P)
				Placebo			BASFI	NS
Steven et al.[105] (1985)	3	24	15/2	D-Penicillamine 125–750mg od	40 (26–55)	16 (8–28)	Overall pain (100cm VAS)	NS
				Placebo	39 (33–58)	9 (1–26)		

a Quality of articles was assessed using the validated instrument of Jadad et al.[11] with a scale of 0–5.

b RCTs with the following outcomes are reported: BASDAI, BASFI, ASAS criteria and pain scores.

c Composite index response defined as an improvement of ≥20% in at least five of the following: (i) severity of morning stiffness (100mm VAS); (ii) physical well-being (100mm VAS); (iii) BASDAI; (iv) BASFI; (v) Health Assessment Questionnaire for spondyloarthropathies; (vi) physician global assessment (100mm VAS); (vii) patient global assessment (100mm VAS). In addition, a responder requires no worsening in any of the scales (<20% worsening compared with baseline values).

ASAS = Assessment in Ankylosing Spondylitis: **BASDAI** = Bath Ankylosing Spondylitis Disease Activity Index; **BASFI** = Bath Ankylosing Spondylitis Functional Index; **NA** = data not provided; **NS** = not significant; **od** = daily; **SD** = standard deviation; **VAS** = visual analogue scale.

ment of AS, particularly for peripheral joint symptoms.[80-82] One large study of sulfasalazine failed to show better efficacy than placebo, but re-analysis of the data revealed that pain scores improved in the subset of patients with peripheral arthritis.[73] There is no evidence of a disease-modifying effect with sulfasalazine.[76] Pamidronate, methotrexate and amitriptyline may alleviate symptoms in some patients. One study provided evidence that pamidronate may be efficacious[86] but confirmation by additional controlled studies is necessary. The evidence for methotrexate is also limited and research results are conflicting.[102,103] The only RCT in which amitriptyline was studied showed improvement in BASDAI but not in pain and fatigue.[104]

Studies with the anti-TNFα agents infliximab and etanercept demonstrated efficacy in symptomatic relief of pain in patients with AS. Both infliximab and etanercept have demonstrated the ability to lead to regression or complete improvement of magnetic resonance imaging-diagnosed entheseal lesions.[94,109] Long-term studies will need to be conducted to determine whether anti-TNFα agents are disease-modifying in AS. Despite the promising clinical effects and possible disease-modifying capabilities, there remain many gaps in the evidence about these agents, including effective starting and maintenance dosages, optimal time for treatment initiation, duration of therapy, and risk factors for adverse effects as well as long-term safety.

The results of this review have to be seen in light of some limitations. Publication bias cannot be ruled out, as only published studies were considered in this review. Additionally, it is possible that reported findings overestimate the benefits of the interventions, since studies with significant results are more likely to get published than studies without significant results, leading to publication bias. There may also be a language bias. It has been suggested that authors are more likely to report positive findings in an international English language journal and negative findings in a local journal.[110,111] Another potential limitation of the review is that study results were not weighted by the sizes of study populations. In certain instances, studies may not have been powered to detect significant differences. Despite extensive searching, it is possible that some RCTs were not identified, especially if they were not listed in MEDLINE. Finally, potentially clinically relevant studies might have been excluded, if they had a Jadad score of <3.

4. Conclusion

In conclusion, nonselective NSAIDs and selective COX-2 agents are effective for pain control in patients with AS, and can be safely used short-term. In patients needing long-term daily intake of an NSAID, one has to weigh the benefits versus the risks of such long-term use.[108] Other proven treatment options include sulfasalazine for the treatment of peripheral joint symptoms. Limited evidence supports the use of pamidronate or methotrexate, which require further studies. The anti-TNFα therapies that have been shown to be very effective for the treatment of both peripheral and axial symptoms in AS seem to be the most promising. Currently, the use of anti-TNFα agents is limited by cost and uncertainty over long-term efficacy and safety.

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