LEADING ARTICLE

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Management of Spondyloarthropathy
New Pharmacological Treatment Options

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Abstract

Spondyloarthropathies (SpA) are a group of inflammatory arthritides classified according to common features of peripheral and spinal arthritis. The conventional anti-inflammatory and disease-modifying or slow-acting anti-rheumatic drugs do appear to be efficacious in treatment of the peripheral arthritis in a comparable fashion to seropositive rheumatoid arthritis, however, their efficacy in axial disease is unproven. This review examines new pharmacological developments in the treatment of SpA including the specific features of sacroiliitis, enthesitis and spondylitis in addition to the peripheral manifestations. The main points that are discussed are new cyclo-oxygenase (COX)-2 specific anti-inflammatories, biological therapies, such as anti-TNF compounds, and novel uses of well-known agents.

Spondyloarthropathies (SpA) are a group of inflammatory arthritides characterised by specific features of axial and peripheral arthritis. SpA include the diagnoses of ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-related arthritis, reactive arthritis (ReA) and undifferentiated spondyloarthropathy (USpA). The classification is based on a number of shared clinical and pathogenetic factors, however, primarily it is on the clinical feature of pattern of skeletal involvement. The treatment of SpA has conventionally depended on the clinical presentations – axial disease (sacroiliitis, spondylitis), peripheral arthritis, enthesopathy or associated features (uveitis, psoriasis, colitis). The treatment comprises a non-drug therapy (physiotherapy and rehabilitation) and drug therapy that can be administered locally or systemically. Conventional treatments have generally been useful for the control of peripheral arthritis but have proven of minimal use in spinal disease.

In this review, we focus on recent advances and novel applications of established drugs. The major recent advances in therapeutic strategies and their efficacies are shown in table I, these include cyclo-oxygenase–specific inhibitors and biological agents, particularly anti-tumour necrosis factor (TNF)-α agents, which appear on magnetic resonance imaging (MRI) study to produce positive responses in spinal joint and entheseal pathology in patients with AS.

1. Anti-Inflammatory Agents

Non-steroidal anti-inflammatory drugs (NSAIDs) are very useful in the symptomatic therapy of patients with seronegative spondyloarthropathy with axial involvement. One of the first NSAIDs recognised as particularly effective in the treatment of SpA was phenylbutazone; however, this has now been withdrawn in most countries because of potential bone marrow toxicity. The other concern for long-term use of NSAIDs is the development of peptic ulcer disease. Conventional NSAIDs act by inhibiting the two isoenzymes of cyclo-oxygen-

Table I. Main drugs used to treat patients with spondyloarthropathies, and the efficacy of each group in peripheral and axial disease

Drug	Efficacy	
	Peripheral arthritis	Axial disease
Anti-inflammatory drugs		
Conventional NSAIDs	+	+
Coxibs	+	+
Corticosteroids		
Local	++	++
Systemic	+/–	+/–
Disease-modifying drugs		
Sulfasalazine/mesalazine	+/++	–
Methotrexate	+/++	–
Infliximab	++/+++	++/+++
Etanercept	++/+++	++/+++
Miscellaneous		
Thalidomide[a]	+/++	+/++
Pamidronate	+	+
Ciprofloxacin	–	–
Doxycycline	–	–

a Only two patients.

Coxibs = cyclo-oxygenase–2 specific inhibitors; **NSAIDs** = non-steroidal anti-inflammatory drugs; – indicates no efficacy; + indicates mild efficacy; ++ indicates moderate efficacy; +++ indicates good efficacy.

ase – COX-1 and COX-2. COX-1 is responsible for the production of prostaglandins important for the maintenance of gastric mucosal integrity, and platelet and renal function, whereas COX-2 is inducible and is responsible for the biosynthesis of prostaglandins at the site of inflammation.

Celecoxib is one of two new highly selective COX-2 inhibitors, which has been shown to improve symptoms of osteoarthritis and rheumatoid arthritis, with no significant increased rates of peptic ulcer disease and no appreciable effects on platelet function compared with placebo.[1-3] Celecoxib has also recently been shown to be effective in improving pain and function in patients with AS.

Dougados et al.[4] were the first to report on the short-term efficacy of celecoxib in the treatment of AS in a recent double-blind, placebo-controlled trial of 246 patients with AS without peripheral synovitis. Patients were randomised to receive placebo (n = 76), ketoprofen 100mg twice daily (90) or celecoxib 100mg twice daily (80) over a 6-week period. All patients had active disease as defined by a pain score ≥40mm, on a 100mm visual analogue scale (VAS) and by an increase in pain of at least 30% after withdrawal of NSAIDs. Primary outcome measures were change in pain intensity (VAS) and change in functional impairment (measured using the Bath Ankylosing Spondylitis Functional Index [BASFI]). Celecoxib and ketoprofen demonstrated efficacy superior to placebo, with a trend in favour of celecoxib over ketoprofen when the two active agents were compared. The mean changes were –27mm, –21mm and –13mm ($p = 0.006$) for pain and –12, –6 and 1 ($p = 0.0008$) for BASFI score in the celecoxib, ketoprofen and placebo groups, respectively.

However, previous studies have suggested that a 6-week clinical trial is not of sufficient duration to detect the optimal dosage of NSAIDs for the treatment of AS.[5] Therefore, further trials of involving the COX-2 specific agents, including those currently in development, for a longer duration and at different dosages are necessary to define the optimal efficacy of these agents in patients and to definitively conclude that they indeed have an improved safety profile.

2. Corticosteroids

Overall, although NSAIDs are effective in reducing pain in most patients with AS, there are patients with refractory SpA who are not responsive to NSAIDs or patients in whom these drugs are poorly tolerated as a result of gastrointestinal complications. Corticosteroids are very powerful anti-inflammatory agents. Intra-articular injection of corticosteroids may be rapidly effective for the treatment of peripheral arthritis and inflammatory sacroiliitis associated with SpA.[6,7] Corticosteroids are particularly useful in patients with adverse reactions to NSAID therapy. Local corticosteroid injections of the sacroiliac joints may be performed using fluoroscopy or computed tomography (CT)-guided techniques to increase the accuracy of drug placement. Although these are therapeutically effective, radiation exposure could be an important disadvantage in certain patients espe-

cially in children, women of childbearing age and during pregnancy. Therefore, in these patients, magnetic resonance imaging (MRI)-guidance offers an important and useful alternative method.

Gunaydin et al.[8] reported in a pilot study that MRI-guided corticosteroid injections into inflamed sacroiliac joints are effective and well tolerated in patients with resistant SpA. They performed 16 sacroiliac joint injections in nine patients (six male, three female) with triamcinolone acetonide 40mg under MRI-guidance. Seven of nine patients reported subjective improvement, which lasted for a mean of 10.8 ± 5.6 months. The mean VAS values were 7.4 ± 0.9 and 3.8 ± 2.1 before and after treatment, respectively. In eight of nine patients the subchondral bone morrow oedema on fat suppressed images resolved at follow-up MRI examinations. Elevations of the erythrocyte sedimentation rate (ESR) and the C reactive protein (CRP) values were seen in two and six patients, respectively, and showed no marked changes after treatment. This indicates that local treatment of sacroiliac joints with a single injection of corticosteroid appears to have little or no systemic effects. This technique could be a useful therapeutic option especially for patients with localised sacroiliac joint disease or young patients in whom radiation exposure is not desirable.

3. Tumour Necrosis Factor-α Antagonists

Anti-tumour necrosis factor (TNF)-α therapy has previously been shown to be effective in patients with rheumatoid arthritis[9,10] and in IBD.[11] TNFα is a key pro-inflammatory cytokine which has been detected in the inflamed bowel mucosa of patients with chronic IBD and the synovium from sacroiliac joints of patients with SpA, including AS. These findings suggest that anti-TNFα therapy directed at neutralising the TNF molecule might be effective in patients with SpA.

The two main biological agents targeting TNFα are the chimeric monoclonal immunoglobulin (Ig)G1 antibody infliximab and the 75kD IgG1 fusion protein etanercept. Infliximab binds directly to both the circulating and membrane bound TNFα molecule, whereas etanercept binds soluble, circulating TNFα.

There are now positive data for infliximab in the treatment of SpA and for both etanercept and infliximab in the treatment of PsA.

3.1 Infliximab

Van den Bosch et al.[12] evaluated the safety and efficacy of a loading dose regimen of three infusions of infliximab in 21 patients with active SpA (ten AS, nine PsA and two USpA). This was a single centre, non-blind, 12-week pilot study in which the patients received infliximab 5mg/kg at weeks 0, 2 and 6. Active disease was defined as at least one manifestation of peripheral arthritis or enthesitis, or inflammatory back pain. No disease modifying anti-rheumatic drugs (DMARDs) were permitted, although stable doses of NSAIDs, corticosteroids (<10 mg/day) and intra-articular corticosteroid injections were allowed. Clinical and laboratory evaluation included patient global assessment of duration of morning stiffness and pain, physician assessment of swollen/tender joint counts and axial involvement, and laboratory markers of inflammation. In addition, in patients with psoriasis, the extent of skin disease was measured with the Psoriasis Area and Severity Index (PASI). A significant reduction of tender and swollen joint count was seen from day 3 onwards, and morning stiffness and pain in the peripheral joints, which was evaluated at day 14, showed significant improvement compared with baseline. There was also significant improvement in skin disease by day 14 in those patients with psoriasis. Although the symptoms of back pain improved, the Schober's test and intermalleolar distance remained unchanged, suggesting the presence of fixed back disease or persistent inflammation. All patients received a second and third infusion, and had sustained and significant improvement in all variables assessed up to week 12 compared with baseline. No clinical or laboratory adverse reactions attributable to the infusion were noted. In conclusion, the treatment of long standing SpA (mean = 17 years) with infliximab led to a rapid,

sustained and significant improvement in both axial and peripheral joint involvement as assessed by global disease parameters.

Subsequent to this, Kuithof et al.[13] reported the safety and efficacy of a maintenance regimen of infliximab 5 mg/kg administered every 14 weeks in the same patients with active SpA as in the initial non-blind trial, over 1 year. Nineteen out of 21 patients completed the study, with a statistically significant decrease of global, peripheral and axial disease manifestations. Two patients changed to another dose administration regimen because of a partial lack of efficacy but were followed up for analysis of safety. Partial relapse of symptoms was reported by three patients (16%) at week 20, 13 patients (68%) at week 34, and 15 patients (79%) at week 48, with the moment of recurrence between 10 and 14 weeks after re-treatment. This indicates that the inflammatory disease activity cannot be controlled continuously with the maintenance regimen of infliximab 5 mg/kg every 14 weeks. Adjustment of the maintenance regimen is warranted but it is not clear whether this can be achieved by decreasing the interval between doses or by increasing the dosage. Twelve minor infectious episodes were observed but no withdrawals occurred due to adverse events. Twelve of 21 patients (57%) developed antinuclear antibodies, out of which four (19%) also had detectable anti-dsDNA antibodies; however, no lupus-like symptoms were described. This study concluded that infliximab is a 'safe' and effective drug in the treatment of SpA over 1-year follow-up. Although recurrence of symptoms was noted before each re-treatment, no loss of efficacy was observed after re-treatment.

The potential beneficial effects of TNFα antagonists on peripheral arthritis in SpA has been further evaluated by Baeten et al.[14] This non-blind, pilot study in eight patients (three AS, four PsA and one USpA) examined the effect of intravenous infliximab 5mg/kg infusions at baseline, week 2 and week 6. All eight patients had active synovitis of at least one knee joint and synovial biopsies were obtained for histological and immunohistochemical analyses at baseline, week 2 (just before the infliximab infusion) and at week 12. Clinical and laboratory evaluation included patient global assessment of pain and morning stiffness, physician assessment of tender and swollen joint counts, and laboratory markers of inflammation. Overall, there was significant improvement in all parameters of patient and physician global assessment, including peripheral synovitis, regardless of the SpA subtype. Histological analysis of the synovial biopsy tissues showed a reduction in the synovial lining layer thickness and of CD55+ synoviocytes. A reduction in vascularity in the sub-lining layer endothelial cell adhesion molecules was also noted, including E-selectin, platelet endothelial cell and vascular cell adhesion molecule-1; however, intracellular adhesion molecule 1 was unchanged. The overall degree of inflammatory infiltration remained unchanged, although the number of neutrophils and CD68+ macrophages in the sub-lining layer was decreased. This could be due to the lymphocyte infiltration as only CD4+ cells decreased, while CD20+ lymphocytes and plasma cells were increased. In conclusion, reduction histologically of inflammatory cells and molecules in the joint tissue were observed, in addition to the clinical benefit of TNFα antagonist therapy on peripheral synovitis in SpA. This study also revealed immunomodulatory mechanisms involving adhesion molecule expression and lymphocyte infiltration, which were different from previous observations in patients with RA and therefore suggested that TNFα antagonism has distinct immunomodulatory mechanism in SpA. These findings may warrant further evaluation in a larger study.

Although infliximab has become a registered therapy for patients with Crohn's disease, it's efficacy for Crohn's arthritis has not been fully evaluated. Van den Bosch et al.[15] treated four patients with refractory Crohn's disease associated with SpA in an expanded access programme of infliximab at a dose of 5mg/kg intravenously. The disease duration of the articular symptoms in these patients ranged from 2 months to 25 years. Two patients had peripheral joint involvement, one had

AS with peripheral arthritis and one had AS with severe inflammatory axial symptoms and generalised 'bamboo' spine. The treatment was well tolerated in all patients and no adverse effects were noted. All four patients had significant improvement in gastrointestinal signs and symptoms, which was accompanied by a rapid fall in CRP values. There was also a significant improvement of axial and/or peripheral arthritis manifestations, related to their SpA. This small, non-blind study has shown that TNFα antagonism is followed by a fast and substantial improvement of articular as well as axial manifestations of Crohn's disease.

USpA is thought to be the second most frequent SpA subset after AS. Approximately 30 to 50% of patients with USpA are at risk of developing AS in the course of the disease. Brandt et al.[16] showed that patients with severe USpA responded to infliximab therapy to a similar extent as patients in their previous study in patients with early AS.[17] Six patients with USpA were included in this study. Three patients received infliximab 3mg/kg and three received 5mg/kg at weeks 0, 2 and 6. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Functional Index (BASFI), the Metrology Index (BASMI), pain on a VAS and quality of life (Short Form-36) were assessed before, during and after treatment. The patients were observed for a total of 12 weeks. Five patients showed significant improvement at day 1 after the first infusion and this improvement was maintained through to week 12. The group of patients who received infliximab 5 mg/kg showed >50% improvement in all activity, function, pain and swollen joint scores. The 3mg/kg dose was less effective, resulting in ≥15% improvement in the outcome variables. Peripheral arthritis, enthesitis and spinal symptoms improved equally with a fall in CRP values in four patients. Health-related quality of life also improved. There were no serious adverse effects or infections. The authors concluded that infliximab is also effective in USpA in the short-term and that a dosage of infliximab of 5mg/kg may be more effective than 3mg/kg for this group of patients. As a significant percentage of patients with USpA develop AS over time, it becomes possible that this transition can be prevented by early TNFα antagonist therapy. Long-term studies with a greater number of participants are necessary to prove this hypothesis.

3.2 Etanercept

Mease et al.[18] recently reported their study with etanercept in the treatment of patients with psoriasis (median duration 18 years) and active psoriatic arthritis (median duration 10 years) defined as ≥3 swollen joints and ≥3 tender or painful joints. They treated 60 patients in a randomised, double blind, placebo-controlled 12-week study with etanercept 25mg or placebo subcutaneously twice weekly. All patients enrolled had active PsA with insufficient response to NSAIDs. Patients were allowed to continue on stable doses of methotrexate (≤25 mg/week) but all other DMARDs were discontinued. Stable doses of corticosteroids (<10 mg/day) were also allowed. Eighty seven percent of patients treated with etanercept met the Psoriatic Arthritis Response Criteria (PsARC) compared with 23% of placebo-treated control patients. The American College of Rheumatology (ACR) preliminary criteria for improvement (ACR20) were achieved by 73% of patients treated with etanercept compared with 13% of placebo recipients. Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of etanercept-treated patients achieved a 75% improvement in the PASI compared with none of the placebo-treated patients. CRP and ESR were significantly decreased in the etanercept-treated group compared with the placebo group. Etanercept was well tolerated with no serious adverse effects noted. Some minor infections occurred in both groups except that more patients receiving placebo developed an influenza-like syndrome. The results showed that etanercept is 'safe' and effective in the short-term treatment of PsA and psoriasis.

3.3 With MRI Assessment

All the above studies (sections 3.1 and 3.2) have shown short-term improvement in clinical and laboratory indices in patients with active SpA when treated with TNFα antagonists. MRI was not used to assess response except by Stone et al.[19] In this non-blind study of 21 patients with active AS (modified New York criteria), 18 patients responded between 2 and 6 weeks after completing a course of infliximab 5mg/kg intravenously at 0, 2 and 6 weeks. There was a >60% improvement in functional variables and also significant improvement of serum inflammatory markers. A subset of nine consecutive patients were selected for MRI examination before and after infusions. Seven patients with imaging studies showed improvement as early as 2 to 4 weeks infusion including those with advanced disease. In one patient with a non-MR compatible cerebral aneurysm clip, ultrasound was proved useful in the evaluation of Achilles tendon, retrocalcaneal bursa and enthesis. MRI has the ability to detect early cartilage changes and bone marrow oedema, which cannot be detected with either CT scan or conventional radiography. Further studies with larger numbers are necessary before the role of MRI in evaluating and quantifying response to treatment can be defined.

In another study, Marzo-Ortega et al.[20] evaluated the effect of TNFα antagonism with etanercept on the clinical manifestations of resistant SpA, and also on axial and peripheral entheseal lesions using MRI. Ten patients with SpA (seven AS, two Crohn's spondylitis, one USpA) who had active inflammatory back pain and peripheral involvement received etanercept 25mg subcutaneously twice weekly for 6 months. Clinical assessments were made using validated instruments. MRI scans of sacroiliac joints, the lumbar spine and affected peripheral joints were performed using T2-weighted fat-suppressed (FS) and T1-weighted FS before and after gadolinium sequences at baseline and at 6 months. Enthesitis and associated osteitis were scored semi-quantitatively in pre- and post-treatment scans. There was a statistically significant improvement in clinical and functional measurements at 6 months. Nine patients had a total of 44 MRI-detectable entheseal lesions at study onset. Eighty-six percent of these lesions either regressed completely or improved over the treatment period with no new lesions developing. This study concluded that TNFα antagonism with etanercept for 6 months is effective in controlling the clinical manifestations of resistant SpA, and is associated with marked improvement of enthesitis and associated pathology as determined by MRI.

4. Mesalazine

Mesalazine (mesalamine) is the 5-aminosalicylic acid (5-ASA) component of sulfasalazine after it is broken down in the large bowel by colonic bacteria to 5-ASA and sulfapyridine. The sulfapyridine moiety is absorbed systemically and has been shown previously to be the active component in the treatment of RA, whereas the 5-ASA moiety remains in the bowel lumen and is believed to be the active component in the treatment of IBD. Sulfasalazine has also been shown to be effective for the treatment of peripheral arthritis in SpA.[21,22] However, it is unclear which component is important in SpA. Two recent papers have attempted to address this issue.

The efficacy and safety of mesalazine in treating SpA has been investigated by Thomson et al.[23] in a non-blind trial of 30 patients with long standing SpA (disease duration, mean 12.7 years) who had not previously received any second-line agents. All patients were treated with mesalamine starting at 500 mg/day for week 1 and increased by 500mg every week to maintenance of 1500 mg/day to week 8. Dose escalation for lack of efficacy was allowed after week 8 of therapy. The duration of the study was 16 weeks with endpoints of patient and physician global assessment, morning stiffness, pain, Dougados Functional Index, physical examination, ESR and CRP. Twenty-nine patients with SpA (26 AS, two chronic ReA and one USpA) completed the study. The one patient who dropped out of the study did so because of an intercurrent respiratory tract infection within 2 weeks of base-

line. Thirteen patients had peripheral joint involvement. There was significant clinical and statistical improvement in all measures including peripheral joint and enthesis counts except for axial range of movement. One third of patients were able to discontinue or decrease the dosage of NSAIDs.

In a similar study, Dekker-Saeys et al.[24] studied the efficacy of mesalazine in 29 patients with SpA in a two-part non-blind trial. In the first part, 20 patients with active SpA who had adverse events or failed treatment with sulfasalazine 2 g/day, were switched to mesalazine 2 g/day for 36 weeks. There were no significant changes in the ESR or patient global assessment at the end of the study. However, 85% of the patients had a beneficial effect as scored by physician global assessment. In the second part, 19 patients with active SpA, who were naïve to sulfasalazine, were treated with mesalazine 2 g/day for 36 weeks. In this group, a significant improvement was seen in the ESR and physician global assessment in 89% but not patient global assessment.

These studies demonstrated improvements in clinical and laboratory measures in patients with SpA treated with mesalazine, supporting it is an active moiety in sulfasalazine in the treatment of SpA. This suggests that mesalazine may be an alternative to patients who are intolerant to sulfasalazine, to those who have sulfa allergies and to men planning to have children in the immediate future. Another benefit of mesalazine is that it does not appear to have the same requirement for blood monitoring as sulfasalazine as per the ACR guidelines. Both studies are relatively small, non-blind clinical trials of short duration, therefore, definitive demonstration of efficacy remains unconfirmed.

5. Pamidronate

Pamidronate (pamidronic acid) is an aminobisphosphonate, which selectively localises to bone; however, it may also possess anti-inflammatory properties. It has been shown previously that it suppresses both antigen- and adjuvant-induced arthritis in animal models.[25] There was also a report of its potential anti-inflammatory effects in patients with RA with variable outcomes.[26-28]

Maksymowych et al.[29] evaluated the potential therapeutic effects of pamidronate in patients with SpA refractory to NSAIDs, using clinical and laboratory outcome variables together with dynamic gadolinium-enhanced MRI (DEMRI). This small pilot study included nine patients with SpA (five AS, three USpA and one ReA). Two patients with AS had concurrent IBD but none had psoriasis. All patients had active peripheral joint synovitis and four of seven patients were currently receiving, or had previously received, DMARDs (sulfasalazine up to 3g/day and methotrexate up to 30mg/week). Intravenous pamidronate 60mg was administered over 4 hours in 500ml of 5% dextrose, on days 1, 2, 14, 28 and 56. There was a significant improvement in clinical and laboratory variables assessed. Mean swollen and tender joint count decreased by 93.8 and 98.2%, respectively, and complete clinical resolution of synovitis was noted in five patients. BASDAI decreased by 44.2%, BASFI by 47.3% and the Global Index (BASGI) by 42.2%. The ESR was reduced by 49.4% and CRP values by 66.9%. Acute lymphopenia accompanied by elevated CRP was noted in eight patients in the 48 hours after first pamidronate infusion. Maximal rate and magnitude of DEMRI signal decreased after therapy, especially in the bone marrow. The treatment was generally well tolerated and follow-up has shown that some patients experienced remission and in those who relapsed, some have responded to re-treatment. However, this is only a preliminary, uncontrolled study with a small number of participants and further evaluation in controlled trials is warranted.

6. Thalidomide

Thalidomide is a drug that selectively inhibits TNFα most probably through inhibition of interleukin (IL)-12 production. Clinical efficacy of this drug has previously been reported in several pathological situations, albeit in small studies and case reports, which may be related to its inhibitory action on these cytokines.[30]

Table II. Main toxicities of drugs used to treat patients with spondyloarthropathies

Drug	Main adverse effects or toxicity
Anti-inflammatory drugs	
Conventional NSAIDs	GI bleeding/ulceration, platelet dysfunction, renal toxicity
Coxibs	Allergy, rash, nausea, abdominal pain
Corticosteroids	Fluid retention, hypertension, Cushing's syndrome, obesity, hirsutism, adrenal suppression, osteoporosis
Potential 'disease-modifying drugs'	
Sulfasalazine	Allergy, granulocytopenia, abnormal liver enzyme levels, azoospermia
Mesalazine	Hypersensitivity
Methotrexate	Granulocytopenia, abnormal liver enzyme values, pneumonitis, teratogenicity
Infliximab	Reactivation of TB, positive ANA response
Etanercept	Infection, demyelination (resembling multiple sclerosis) or possibly neuritis
Miscellaneous	
Thalidomide	Granulocytopenia, neuritis, teratogenicity
Pamidronate	Infusion reactions – arthralgia, myalgia; acute lymphopenia
Ciprofloxacin	Nausea, diarrhoea, rash
Doxycycline	Tooth discolouration, enamel hypoplasia, reduced fibula growth rate

ANA = antinuclear antibody; **Coxibs** = cyclo-oxygenase–2 specific inhibitors; **GI** = gastrointestinal; **NSAIDs** = Non-steroidal anti-inflammatory drugs; **TB** = tuberculosis.

In a case study Breban et al.[31] reported the efficacy of thalidomide in two human leucocyte antigen (HLA)-B27–positive patients with severe refractory AS. Both patients were in their early twenties and had severe AS affecting both axial and peripheral joints. The AS of the first patient had been resistant to many therapeutic interventions including NSAIDs, pulse methylprednisolone, sulfasalazine, methotrexate, intramuscular gold and local corticosteroid injections in affected joints. The second patient had received only NSAIDs and sulfasalazine. Both patients were treated with thalidomide at 300 mg/day, with an escalating dose from 100 mg/day in the first patient. There was a dramatic improvement in clinical and laboratory findings. Axial and peripheral pain and stiffness disappeared within 6 months while the ESR and CRP values normalised within 3 months. The first patient experienced a serious adverse event with the development of granulocytopenia. However, this resolved quickly once the thalidomide was discontinued; unfortunately this was followed by a rapid recurrence of symptoms and markers of inflammation. Thalidomide was reintroduced at a lower maintenance dose of 150mg to 200mg daily and the granulocytopenia did not recur; however, the efficacy may have been reduced.

The reports of the use of thalidomide are very preliminary and only in a very small number of cases. Therefore, results should be interpreted with caution. At present, thalidomide deserves further clinical investigation but extreme caution must be taken, in particular in females of childbearing potential because of the proven teratogenicity of this agent, and also the delayed neuropathy.

7. Antibacterials

Eradication of candidate triggering microbes in patients with ReA with antibacterials would appear to be a logical therapeutic approach. Some studies have failed to demonstrate that short-term antibacterial treatment influences the course of post-enteric ReA. Long-term studies of antibacterials suggest treatment of chlamydia-triggered acute ReA may lead to more rapid recovery, less chronicity and prevent recurrences of chlamydia-induced ReA, antibacterial treatment for recurrences of chlamydial urethritis may also be of value. However, the benefits of antibacterial treatment in chronic forms of ReA and in the wider spectrum of SpA remain controversial.[32-35]

Ciprofloxacin is a synthetic 4-quinolone derivative with bactericidal activity against a wide range of Gram-negative and Gram-positive bacteria. It is effective against most bacteria linked to the pathogenesis of ReA such as *Salmonella* spp., *Campylobacter* spp., *Yersinia* spp. and *Chlamydia* spp.[36] Ciprofloxacin also has a good penetration into the inflamed tissues and, thus, it would be a reasonable therapeutic option for the treatment of ReA.

Yli-Kerttula et al.[37] evaluated the efficacy, safety and tolerability of long-term treatment with ciprofloxacin compared with placebo in patients with acute ReA associated with proven gastrointestinal or urogenital infection. Patients with ReA (n = 71) with disease duration of less than 3 months after diagnosis were treated with ciprofloxacin 500mg or placebo twice daily for 3 months in a multicentre, double-blind, randomised study. Clinical assessments were completed periodically up to 12 months. Study endpoints included clinical, laboratory and patient self-assessments. Complete recovery (defined as normal global assessment, laboratory parameters and joint examination) was also determined. No statistically significant differences were found between the ciprofloxacin and the placebo group, and both tended to improve. In addition, there was no significant difference between the enteroarthritis and uroarthritis groups in this well designed study, which concluded that a 3-month course ciprofloxacin has no benefit over the placebo.

In another randomised, triple-blind, placebo-controlled clinical trial,[38] 60 patients (aged between 18 and 65 years, with chronic ReA or SpA with symptoms for at least 4 months) were randomly allocated to receive doxycycline 100mg twice daily (n = 30) or placebo (30) for 3 months. Pain and functional status measured by a self-administered Arthritis Impact Measurement Scales Version 2 (AIMS 2) quality of life questionnaire formed the primary study endpoints. Secondary endpoints were pain and functional status at 6 and 12 months, 3 month rheumatologist assessed joint count, pain and arthritis activity, and treatment efficacy in those with previous exposure to *Chlamydia* spp. Only 37 patients (16/30 receiving doxycycline and 21/30 receiving placebo) were evaluated at 3 months, with no improvement on pain scores or composite functional change scores with doxycycline. There were also no differences in secondary study end points, and no apparent treatment effect in patients with previous chlamydia infections, concluding that doxycycline is not an effective treatment for chronic ReA or undifferentiated seronegative arthritis.

8. Conclusions

It is clear from the small, non-blind studies in patients with SpA and the one substantial controlled study of patients with PsA that TNFα antagonists (infliximab and etanercept) show considerable promise in the treatment of peripheral and axial disease. Indeed, these biological agents are the first disease-modifying drugs to show a significant benefit for both spinal and peripheral arthritis in patients with SpA. Furthermore, these treatments have been associated with a low incidence of adverse events within these study protocols. However, the increase in the number of cases of

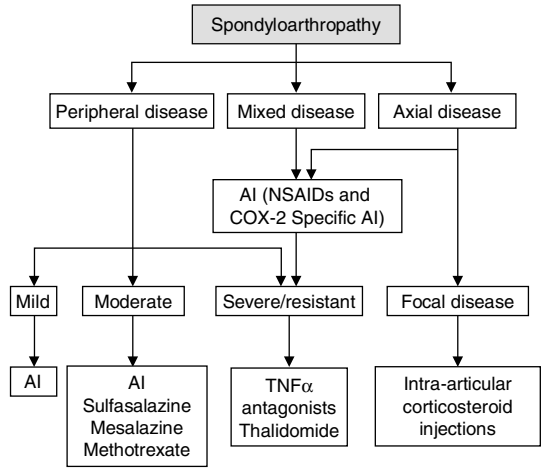

Fig. 1. Treatment algorithm for patients with spondyloarthropathy. **AI** = anti-inflammatories; **COX** = cyclo-oxygenase; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **TNF** = tumour necrosis factor.

Mycobacterium tuberculosis infection following infliximab therapy,[39] and the increase in cases of polyneuritis similar to multiple sclerosis or transverse myelitis following etanercept treatment, have only become noticeable in post-marketing surveillance. The long-term benefits and possible adverse effects (table II) over prolonged treatment periods with these agents will be closely monitored. The other miscellaneous new treatments appear to offer improvements in safety with little advance in efficacy. Although thalidomide may have a role in some patients with severe disease, it is unlikely to become the disease-modifying treatment of first choice. It is disappointing that antibacterial therapy has not shown efficacy, as might have been expected in particular in post-infectious ReA. Figure 1 shows a possible algorithm for the treatment of spondyloarthropathies.

The future of drug development appears to favour biological therapies because of the increased specificity and reduced adverse effects, drugs such as IL-1 receptor antagonists and new anti-TNFα molecules are also currently under study in the treatment of patients with SpA.

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