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Disease Controlling Antirheumatic Therapy in Spondyloarthropathy

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ABSTRACT. The management of spondyloarthropathy (SpA) is based more on clinical presentation (axial *vs* peripheral involvement) than on actual disease diagnosis. Treatment is aimed at controlling inflammation, ankylosis, and abnormal posture. Nonsteroidal antiinflammatory agents are the cornerstone of treatment for patients with axial involvement. If these do not work, disease controlling antirheumatic therapy is usually prescribed. Several drugs, particularly sulfasalazine, produce clinically significant improvement in patients with articular peripheral involvement. In contrast, the therapeutic options for patients with refractory axial involvement are very limited. For this group, "potential" (pamidronate, thalidomide) or "specific" (infliximab) tumor necrosis factor blockers are of potential interest and deserve further evaluation. Therapeutic efficacy is monitored chiefly according to clinical variables, although biochemical markers such as C reactive protein are also helpful. (J Rheumatol 2001;28 Suppl 62:16–20)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SPONDYLOARTHROPATHY
DISEASE CONTROLLING ANTIRHEUMATIC THERAPIES

The group of diseases collectively labeled as spondyloarthropathy (SpA) consists of several disorders: reactive arthritis, psoriatic arthritis, arthritis related to inflammatory bowel disease (IBD), a subgroup of juvenile chronic arthritis, and ankylosing spondylitis (AS) (Table 1). The prototype of this group of interrelated disorders is AS[1]. Classification criteria (Table 2) that support a diagnosis of spondylarthropathy include inflammatory spinal pain or synovitis (asymmetric or predominately in the lower limbs), and at least 1 of the following: positive family history, psoriasis, inflammatory bowel disease, urethritis or acute diarrhea, alternating buttock pain, enthesopathy, or sacroiliitis as determined from radiography of the pelvic region[2].

Recent epidemiologic studies from Europe indicate that SpA is not uncommon. In Berlin, for example, Braun and colleagues[3] found a 13.6% prevalence of SpA in the B27-positive population and from this, calculated a 1.9% prevalence of this disorder in the general population. Another study, from Brittany, found the prevalence of SpA in the general population (0.47%) to resemble that of rheumatoid arthritis (RA) (0.62%)[4].

Spondyloarthropathy produces a variety of signs and symptoms, including spinal stiffness, extra-spinal joint disease, and enthesiopathic lesions (Table 3). Management of SpA is related more to the patient's clinical presentation (axial *vs* articular or extraarticular involvement) than to the precise disease diagnosis[5].

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Table 1. Diseases belonging to the category of SpA.

Ankylosing spondylitis
Arthritis associated with inflammatory bowel disease
Reactive arthritis
Psoriatic arthritis
Undifferentiated spondyloarthropathy

Table 2. Criteria for classification of SpA.

Inflammatory spinal pain or
Synovitis (either asymmetric or predominately in the lower limbs)
And one or more of the following:
Positive family history
Psoriasis
Inflammatory bowel disease
Urethritis, cervicitis, or acute diarrhea presenting one month before arthritis
Buttock pain alternating between right and left gluteal areas
Enthesopathy
Sacroiliitis

Awareness of the prevalence and clinical presentation of spondyloarthpathy is very important to apply in daily practice because it permits earlier diagnosis, facilitates patient education, and allows more accurate prognostication[6].

AXIAL INVOLVEMENT

Management objectives. The therapeutic objectives for patients with axial involvement are to reduce and/or prevent deleterious clinical effects associated with the 3 main characteristics of SpA: inflammation, ankylosis, and abnormal postures (Table 4).

Monitoring. The ASAS (Assessment of Ankylosing Spondylitis) Working Group has recently proposed that the

Table 3. Clinical features of SpA.

Extraarticular features
Acute anterior uveitis
Endocarditis
Genetic background
Family history
HLA-B27 antigen
Rheumatologic manifestations
Axial involvement
Enthesiopathy
Peripheral articular involvement
Specific manifestations
Inflammatory bowel disease
Psoriasis

efficacy of disease controlling antirheumatic therapies (DCART) be evaluated according to the following primary domains, or criteria: pain, functional disability, spinal mobility, stiffness, acute phase reactants, radiographic spine findings, and fatigue[7].

ASAS and various international societies including OMERACT IV (Outcome Measures in Rheumatoid Arthritis Clinical Trials) and ILAR (International League Against Rheumatism) have recommended specific instruments for measuring each of these domains in both clinical research studies and daily practice[8].

However, there are 2 areas where there is not consensus among ASAS for specific instruments: the performance of radiographic spine systems and the clinical relevance of acute phase reactants. Several systems, incuding the BASRI (Bath Ankylosing Spondylitis Radiology Index) and SASSS (Stoke Ankylosing Spondylitis Spine Score), have been proposed for evaluating the structural severity of SpA through spinal radiographs[9,10]. Most of these systems quantify the level of spinal ossifications. The interobserver reliability and/or the sensitivity to changes of these methods appears to be moderate.

An increase in C-reactive protein (CRP) is observed in 40% of patients with SpA who have axial involvement[11]. Elevated CRP levels are associated with more severe disease and probably predict structural deterioration[10].

EXPERIENCE WITH DCART

Nonsteroidal antiinflammatory drugs (NSAID). These are considered the cornerstone of drug therapy for patients with SpA. Axial involvement is probably the clinical presentation that responds the most dramatically to NSAID. As the NSAID have usually been clinically evaluated in patients with rheumatoid arthritis (RA), the recommended dosage for inflammatory rheumatic diseases should be the dosage used in AS. Whether this short term symptomatic effect will correlate with improved longterm prognosis remains unknown.

Another question to emerge recently is whether SpA, and especially AS, have become less severe since the introduction and longterm use of NSAID. This question is particularly important to clinical patient management: a disease controlling effect would support a role for daily NSAID therapy, while the absence of such an effect would limit the use of NSAID to control of acute flares[4].

The COX-2 specific inhibitors offer an additional option in the drug armamentarium for SpA. A 6 week randomized, double blind placebo controlled study completed at our institution with the COX-2 specific inhibitor, celecoxib, showed a greater decrease in pain and functional impairment in the celecoxib and ketoprofen groups than placebo, with a trend in favor of celecoxib[12].

Corticosteroids. There are few, if any, studies evaluating corticosteroids in patients with axial involvement of SpA. However, there is evidence that oral corticosteroids are of minimal to no use to patients with AS, and that chronic administration causes unwanted side effects[4].

Second line drugs. Studies evaluating the effects of second line drugs in AS are difficult to interpret because most of them give no information concerning the patient's clinical presentation at study entry (axial and/or peripheral articular involvement). The second line drugs are commonly prescribed for patients with refractory peripheral articular involvement. But do they have a role in resolving axial involvement?

Sulfasalazine. Sulfasalazine is the most studied second line drug in SpA. The results of most investigations show benefit[13-17]. The results of a randomized placebo controlled double blind multicenter study of patients with SpA showed that sulfasalazine had greater efficacy than placebo in the change in pain, morning stiffness, physician and patient's overall assessments, and laboratory markers of inflammation[14].

In clinical practice, sulfasalazine, 2000 to 3000 mg daily,

Table 4. The 3 main clinical features of SpA.

Clinical Feature	Comments
Inflammation	Responsible for subjective symptoms of pain and morning stiffness as well as such objective clinical measurements as reduction in spinal mobility
Ankylosis	Causes a reduction in spinal and thoracic mobility that can hamper performance of daily activities and reduce chest expansion and respiratory capacity, respectively. Ankylosis can occur even in the absence of clinical symptoms of inflammation, although this is rare
Abnormal posture	Impairs mobility and function; results from inflammation and ankylosis

can be proposed to patients with symptomatic refractory axial involvement with several caveats. Use a "go low go slow" approach to minimize gastrointestinal side effects such as nausea and abdominal pain. The enteric-coated formulation of sulfasalazine (the only one studied and approved for the treatment of RA in the USA) improves GI tolerability and results in better patient acceptance[18]. Reserve the drug for patients who are refractory to NSAID (who have failed on 3 to 4 different NSAID administered at an optimal dosage for at least 2 to 3 weeks each). Inform the patient that achievement of full therapeutic effect will require 2-4 months of therapy. For the first few weeks, administer sulfasalazine in combination with an appropriate NSAID. Administer sulfasalazine for at least 16 weeks before evaluating its efficacy.

Pamidronate. The bisphosphonates are synthetic analogs of pyrophosphates, which are potent inhibitors of bone resorption. Although bisphosphonates were initially given because of their potent antiinflammatory effects, they now have a major role in treating disorders of bone metabolism such as Paget's disease, metastatic bone disease, and osteoporosis, which is common in patients with severe AS[19].

Recent work suggests that bisphosphonates may suppress the generation of proinflammatory cytokines such as interleukin 1 (IL-1), tumor necrosis factor (TNF)-α and IL-6, and that they may blunt the antigen presenting function of macrophages[20]. Open uncontrolled studies suggest that an intravenous infusion of pamidronate, 30 mg once a month for 3 months increased to 60 mg once a month for an additional 3 months, might improve the clinical condition of patients with AS[21]

Thalidomide. This drug selectively inhibits production of both TNF-α (presumably by enhancing degradation of messenger RNA), and IL-12[22,23]. Results of a preliminary open study suggest that thalidomide, given at selectively high doses of up to 300 mg/day, might dramatically improve the patient's condition, as assessed by both clinical and biologic (decrease in CRP) variables[24]. The main adverse event observed at this dosage was drowsiness[25].

TNF-blockers. The results of 2 recent open uncontrolled studies strongly suggest that infliximab, a chimeric human murine monoclonal class IgG1 antibody, dramatically improves axial signs and symptoms of spondyloarthropathy. The efficacy of anti-TNF-α has been clearly established in patients with RA, who take infliximab with methotrexate (MTX) to avoid the formation of antiidiotype antibodies[26]. The efficacy of anti-TNF-α in Crohn's disease is particularly of interest because Crohn-like gut lesions have been detected in a significant percentage of patients who have SpA[27,28]. Infliximab is administered without MTX to patients with Crohn's disease.

In recent open trials from Belgium and Germany, infliximab (without MTX) was administered at a 5 mg/kg dosage at baseline and at 2 and 6 weeks thereafter[29,30]. A dramatic response occurred in activity, function, and pain scores a few hours after the first injection that appeared to be maintained for at least 10 weeks. These relevant clinical results were accompanied by normalization of the biological markers of inflammation; specifically, a decrease in levels of CRP.

Such results are very encouraging since the therapeutic options for patients with refractory axial involvement of AS are very limited. Further studies are clearly needed to confirm the results of these promising preliminary studies, to evaluate both the short term and longterm safety profile of such treatment, and to better define the clinical profile of the patients for whom DCART therapy should be considered[31].

PERIPHERAL ARTICULAR INVOLVEMENT

Objectives. The objectives of treating patients with SpA who have articular involvement are similar to those of treating persons with axial involvement. Therapy is aimed at reducing and/or preventing the deleterious effects of the 3 main clinical characteristics of the disease: inflammation, cartilage breakdown, and abnormal postures.

Monitoring. Patients with peripheral articular involvement of SpA are monitored very similarly to those with RA. The number of tender and swollen joints are interpreted as a reflection of underlying disease activity.

Experience with DCART. DCART are indicated in the case of persistent (6 weeks) oligo and/or polyarticular involvement refractory to either local corticosteroid or oral NSAID therapies.

Sulfasalazine. Metaanalysis of data from 5 randomized controlled trials suggests that sulfasalazine is a safe and effective drug for short term (3 to 6 months) treatment of patients with AS[32]. One randomized, double blind, multicenter study in patients with AS reported that sulfasalazine did not seem to be more effective than placebo in patients with chronic longstanding disease. However, patients with AS with associated peripheral arthritis showed improvement that favored sulfasalazine[17].

The mechanism by which sulfasalazine works in AS remains unresolved. For example, it is still unclear which of its constituents, sulfasalazine or sulfapyridine, is the active moiety. A 26 week controlled study comparing the effects of sulfasalazine, 2 g/day, and sulfapyridine, 1.25 g/day and 5-aminosalicylic acid (ASA) 800 mg/day, was conducted in 90 patients with active AS[33]. Study results indicated that sulfapyridine is the active component of sulfasalazine in AS. Patient outcome appeared to be better in the sulfasalazine group compared with sulfapyridine alone perhaps suggesting the importance of a common sulfonamide structure for clinical efficacy. On the other hand, a recently open study reports that olsazaline, a dimer of 5-aminosalicylic acid, might be effective in AS[34].

Most of these studies clearly emphasize that the most impressive effects of sulfasalazine are observed in patients with peripheral articular involvement. However, there are at least 3 reasons not to prescribe this drug routinely for all

patients with peripheral articular involvement: episodes of articular involvement usually resolve spontaneously within a few weeks; generally, only a few joints are affected; and the longterm evolution of peripheral articular involvement in SpA differs from that of RA. In RA, discontinuation of sulfasalazine after several months of treatment usually leads to flare several weeks later. This is far from the rule in SpA. A lack of recurrence raises the question of whether sulfasalazine should be continued in the setting of clinical remission. My colleagues and I discontinue sulfasalazine after a 2 year period of remission and then monitor patients clinically and biologically each month. In the event of disease flare, we reinstate sulfasalazine.

MTX. Most trials (usually not placebo controlled) of MTX indicate beneficial results in patients with SpA. MTX appears to be the drug most frequently used in this indication probably because it improves psoriasis, psoriatic arthritis, and is a drug of choice for managing RA[35,36]. MTX is administered at a dosage similar to its use in RA, 0.2 to 0.3 mg/k/week.

TNF blockers. All the studies evaluating either the potential TNF blockers, such as pamidronate[21] and thalidomide[24], or the specific TNF blockers, such as infliximab[29,30], strongly suggest that patients suffering from a peripheral articular involvement of SpA might benefit from these drugs, particularly the specific TNF blockers.

Antibiotics. Antibiotic treatment of the triggering infection is recommended if the offending organism can still be identified after the onset of arthritis. Antibiotics are probably worthwhile for recurrent *Chlamydia* urethritis to prevent repeat episodes of *Chlamydia* induced reactive arthritis[37].

The value of antibiotic treatment in chronic forms of reactive arthritis remains unresolved. There are findings suggesting some benefit[38]. However, more research with sufficient numbers of patients is still needed.

EXTRAARTICULAR FEATURES

There are 2 categories of extraarticular features observed in patients with SpA. The first one corresponds to the extraarticular manifestations that are specific to the disease subgroup, the skin lesions of psoriatic arthritis and the gut lesions of arthritis related inflammatory bowel disease, for example. The second category corresponds to extraarticular features, such as anterior uveitis, that are observed whatever the subgroup.

Usually, a drug is of potential benefit regardless of how the disease presents clinically. For example, sulfasalazine, a drug of choice for managing gut lesions of inflammatory bowel disease, has some effect on the skin lesions of psoriasis. A particular indication for DCART might be the prevention of recurrent episodes of acute anterior uveitis. Some open controlled studies, as well as the results of a large multicenter study examining the effects of sulfasalazine on the rheumatologic manifestations of SpA, suggest that this drug might also be of interest in reducing both the severity and frequency of recurrent episodes of acute anterior uveitis[14,39].

CONCLUSION

The group of diseases collectively labeled SpA are a common form of inflammatory rheumatism. Therapeutic options for axial symptoms, peripheral arthritis, and extraarticular involvement are limited. In addition to sulfasalazine and MTX, new therapeutic approaches that include TNF blockers are very promising. The new antirheumatic drugs should be more adequately and systematically evaluated in patients having various clinical manifestations of SpA.

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