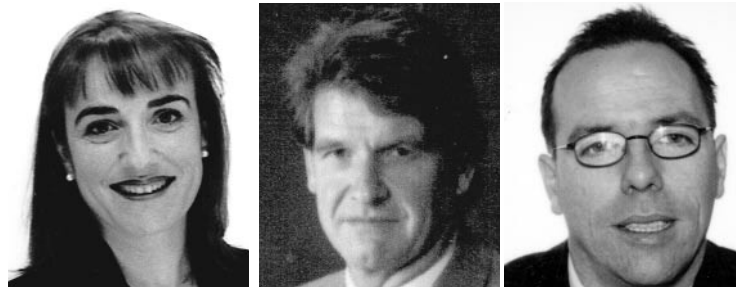


# The Concept of Disease Modification in Spondyloarthropathy



The concept of disease modification was first introduced in rheumatoid arthritis (RA) and refers to the ability of the so-called disease modifying antirheumatic drugs (DMARD) to affect the underlying disease process<sup>1</sup> and prevent joint damage. Traditionally, the term DMARD has been applied to various drugs that have a modest or moderate effect on synovitis suppression and bone damage retardation<sup>2,3</sup>. However, the advent of powerful biologic agents such as infliximab and etanercept has confirmed a long held view in RA — that is, providing synovitis is adequately suppressed over time, then bone damage is minimal<sup>4,5</sup>. By contrast, a different scenario has applied in ankylosing spondylitis (AS) and the related spondyloarthropathies (SpA), where disease modifying effects of drugs have yet to be defined. In recognition of this, investigators have chosen terminology carefully and use terms such as “symptom modifying drugs” or “disease controlling antirheumatic therapy” (DCART)<sup>6</sup>. This article reviews the basis for this discrepancy between RA and SpA and proposes that in the light of recent advances in imaging and therapeutics in SpA, the concept of disease modification may now be applied to these diseases.

Disease pathogenesis differs between RA and SpA (Table 1). For example, in RA, cartilage and bone destruction secondary to synovitis within small synovial joints is the primary disease outcome and it correlates with loss of function. Bone damage is measured by conventional radiography, a well validated tool in RA, and its prevention is the desired treatment goal. In contrast, AS and the SpA have a predilection for the spine and large synovial joints, where

prominent reparative processes with bone sclerosis and new bone formation usually occur in addition to bone destruction. These reparative bone changes are responsible for joint ankylosis and cause disability in these patients. So, ideally it is not the measurement of progressive radiographic destruction, but rather the failure to develop ankylosis and bone deformities, that would represent true disease modification in AS. However, it is at these sites, particularly at the spine, where conventional radiography, the traditional imaging method used in SpA, suffers from a number of limitations. First, radiography lacks the sensitivity to show small focal changes in skeletal calcium content in large joints. Second, the development of radiographic bone damage may be slow in AS, taking up to at least a decade to manifest<sup>7</sup>. These factors have hampered the development of the concept of disease modification in AS and SpA.

However, there have been two advances in rheumatology in the last decade that should allow for this to be developed. These are (1) the increasing use of magnetic resonance imaging (MRI), and (2) the advent of new therapies that suppress inflammation in SpA. Fat suppression MRI techniques are excellent for showing sacroiliitis, enthesitis, and osteitis<sup>8-10</sup>, which are the characteristic primary spinal lesions in AS and which are also common within and adjacent to synovial joints. Biologic antiinflammatory agents such as infliximab or etanercept were first proven to be highly effective in RA<sup>11,12</sup>, and it is now emerging that they are also efficacious in AS and all subtypes of SpA. Indeed, evidence so far suggests that their efficacy in controlling

Table 1. Differences of disease pathogenesis between RA and SpA.

	RA	AS and SpA
Pathology	Synovitis	Enthesitis, osteitis, and synovitis
Target tissue	Synovium	Entheses, bone, and ?synovium
Affected sites	Synovial joints	Spine and large synovial joints
Outcome	Joint erosions, cartilage loss	New bone formation, erosion, and cartilage loss
Outcome measures		
Radiography	Detects bone erosions within 2 years of disease in 80% of patients	Detects sclerosis, proliferative new bone formation, which in the spine can take up to 10 years from disease onset
MRI	Synovitis primary, focal periarticular bone erosion secondary	Diffuse bone edema at enthesal sites primary. Synovitis secondary?

signs and symptoms in patients with chronic AS<sup>13</sup>, psoriatic arthritis<sup>14</sup>, and the SpA of Crohn's<sup>15</sup> is comparable if not superior to RA, suggesting a central role for proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in the pathogenesis of these diseases. Our own experience with etanercept suggests that this drug is very efficacious in suppressing axial and peripheral joint disease even in established cases that have proven resistant to conventional therapies. We have shown using MRI that the primary lesion in the spine, enthesitis and osteitis, neither of which were apparent on radiography, either completely regressed or improved after treatment, and this was accompanied by major improvements in clinical and laboratory measures of disease activity, including a fall in the acute phase response as measured by the C-reactive protein<sup>16</sup>. These data confirm that different anatomical regions of inflammation and not just synovitis respond to anti-TNF therapy. Similarly, other investigators have recently used MRI to monitor the efficacy of other biologics such as infliximab<sup>17</sup> and other novel agents and have reported similar findings<sup>18</sup>.

Although MRI identifies a clear pathology occurring at the bone marrow and related enthesis as well as the synovial joints, there are still a number of unresolved issues. First, the relationship between inflammation and bone damage in AS is not fully defined and the question remains: is there a linear relationship between inflammation in AS and other SpA and subsequent joint ankylosis? The original histological studies by Bywaters<sup>19</sup> suggested that bone ankylosis may be independent of the associated inflammation, although these observations were based on a limited number of histological sections. Also, experimental models of AS and in particular the ANKENT mouse have prominent joint fusion without much discernible inflammation<sup>20</sup>. It is noteworthy, too, that diffuse idiopathic skeletal hyperostosis (DISH), a disease that can sometimes resemble AS, is not regarded as having an inflammatory component. Even though enthesitis is regarded as the primary pathological abnormality in SpA<sup>21-23</sup>, definitive proof of the relationship between enthesitis and osteitis and bone ankylosis is still lacking. However, recent MRI and radiographic studies in early disease<sup>24</sup> indicate that MRI bone changes predate radiographic abnormalities, suggesting that in AS, enthesitis and osteitis is primary and bone changes such as sclerosis or syndesmophytes are secondary. Therefore, to demonstrate unequivocally that these new drugs constitute true DMARD in SpA, it will be necessary to show that sustained reversal of the inflammation at the enthesis and adjacent bone prevents subsequent radiological fusion of the joint and associated loss of function. Evidence so far is reassuring, as studies conducted to date with biologic agents have shown dramatic response, even when used to treat patients where a degree of irreversible joint fusion had already occurred, suggesting that there is room for disease modification even at later stages. However, confirmation of this can only be

achieved by the systematic and controlled longitudinal observation of large cohorts of patients. From a theoretical perspective, inflammation generally hinders new bone formation and tends to favor the development of osteoporosis. It will therefore be important to carefully document that suppression of inflammation at the spinal entheses is not associated with increased new bone formation with joint fusion and spinal ankylosis.

MRI is increasingly used as a research tool and should be able to address the effects of other drugs in AS and SpA. Bisphosphonates have been shown to cause regression of MRI determined osteitis<sup>18</sup>, and could potentially have modifying properties in SpA; this awaits further MRI studies. Similarly, it is unclear whether the excellent response noted to nonsteroidal antiinflammatory agents in AS could be associated with regression of the enthesitis associated bone pathologies. The ability to image the primary site of pathology with MRI may also facilitate the development and validation of biomarkers, which could be a simpler way of assessing disease modification in SpA, as Maksymowych, *et al* have demonstrated in their study<sup>25</sup>.

There is now growing anatomical and therapeutic evidence to introduce the concept of disease modification in SpA. This is based on the fact that new and more potent anti-inflammatory agents are emerging and that sensitive imaging techniques such as MRI can be used to measure regression of inflammation at the different sites of disease. Confirmation that suppression of MRI determined osteitis prevents subsequent bone ankylosis could herald a new era for the appraisal of therapies in SpA, whereby drugs will be initiated based on the evidence for their effect at the primary site of disease in SpA rather than on a successful track record in the therapy of RA, as has been the case until now.

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