Abstract: Spondyloarthritis (SpA) is an inflammatory disease of the spine, the peripheral joints and the entheses and shares some clinical features with rheumatoid arthritis (RA). Chronic inflammation of musculoskeletal structures leads to disease symptoms such as pain and stiffness and structural changes in the bone tissue. Furthermore, therapies for SpA are based on those for RA, which attempt to inhibit synovial inflammation that leads to retardation or even arrest of structural damage. However, in SpA, the bone tissue directly exposed to inflammation (osteitis) is the trabecular bone of the vertebrae, but not the cortical bone surface as in RA (synovitis). Therefore, the success of treatment strategies for structural changes in RA may not be appropriate for SpA. In this article, the authors discuss the pathophysiology of structural damage in SpA and concepts for the preservation of the physiologic bone architecture in patients with SpA.

Key Indexing Terms: Spondyloarthritis; Bone formation; Syndesmophytes; Bone remodeling; Structural damage. [Am J Med Sci 2011; 341(4):269–271.]

Spondyloarthritis (SpA) is an inflammatory disease of the spine, the peripheral joint and the entheses. Despite major differences, SpA shares a common clinical feature with rheumatoid arthritis (RA): chronic inflammation of musculoskeletal structures not only leads to disease symptoms such as pain and stiffness but also elicits structural changes in the bone tissue adjacent and distant from the inflammatory disease process. Bone erosion is the typical skeletal complication of RA, whereas SpA is characterized by bony overgrowth leading to ankylosis of axial joints and the intervertebral spaces. Our therapeutic concepts in both SpA and RA are based on the attempt to inhibit inflammation as best as possible, which dampens the clinical symptoms arising from inflammation and prevents structural damage. In RA, this concept has been proven highly successful; thus, effective control of synovial inflammation allows retardation, or optimally, arrest of structural damage. When this concept is applied to SpA, however, success is far less established, and it is yet unclear which strategy is best to prevent structural damage in SpA. In this article, we discuss the pathophysiolog of structural damage in SpA and concepts for the preservation of the physiologic bone architecture in patients with SpA.

THE RELATION OF INFLAMMATION TO STRUCTURAL DAMAGE

“Low inflammation leads to low structural damage” is the concept we have learned from RA. At first sight, this concept holds true for SpA. A tighter therapeutic regimen with continuous use of nonsteroidal anti-inflammatory drugs is more effective in retarding structural progression in SpA than a more “laissez-faire” strategy that allows nonsteroidal anti-inflammatory drugs only on demand.1 This concept, however, is challenged by the failure of all 3 approved tumor necrosis factor (TNF) inhibitors to retard the progression of structural changes in SpA more effectively than conventional nonbiologic therapy.2– 4 At first sight, this finding may be surprising, because TNF inhibitors show a strong anti-inflammatory potential in SpA. TNF inhibitors not only improve the signs and symptoms of disease such as pain, stiffness and impaired physical function but also effectively ameliorate the inflammatory changes in the spine and sacroiliac joints, which can be visualized by magnetic resonance imaging. However, the concept that effective control of inflammation in SpA automatically leads to a retardation of the structural bone changes does not hold true for this disease. The relation of inflammation and structural changes in SpA seems to be more complicated than in RA.

The observation that inflammation induces new bone formation is rather surprising, because inflammation is considered a deleterious condition for bone. Inflammatory diseases such as RA, systemic lupus erythematosus and inflammatory bowel disease are all associated with bone loss leading to premature osteoporosis.5 Moreover, when inflammation is emerging adjacent to bone tissue, such as the case of synovitis in RA, local bone damage accumulates rapidly in addition to systemic bone loss. Interestingly, SpA is not completely different per se. Patients with SpA develop osteoporosis in the vertebral bodies and exhibit an increased fracture risk, suggesting that chronic inflammation in SpA leads to loss of trabecular bone mass. Vertebral osteoporosis may be directly linked to the formation of inflammatory infiltrates in the bone marrow of patients with SpA and can be detected as spondylitis on magnetic resonance imaging scans. Indeed, histologic examinations of bone sections from the spine of patients with SpA show an accumulation of osteoclasts in the bone marrow and the formation of inflammatory infiltrates.6– 7

LYMPHOCYTES AND THE ROLE OF OSTEOCLASTS IN INFLAMMATION

Accumulation of lymphocytes in the bone marrow is likely to be the reason for the generation of osteoclasts, because activated lymphocytes are the primary source of receptor acti-
vator of nuclear factor kappa-B ligand, a molecule that drives osteoclast differentiation. Vertebral osteoporosis and resorption of trabecular bone thus seems to be the direct consequence of inflammation. This notion highlights a major difference between SpA and RA: in SpA, the bone tissue directly exposed to inflammation (ostitis) is the trabecular bone of the vertebrae, whereas it is the cortical bone surface in RA that is subject to direct attack from inflammatory tissue (synovitis). Furthermore, cortical bone changes in SpA do not represent bone damage by exposure to inflammatory tissue; instead, they can be considered as skeletal response to inflammation because these changes (a) emerge at sites distant from inflammatory tissue involving predominantly periosteal sites not directly exposed to ostitis and (b) are characterized by anabolic rather than catabolic changes.

**ANABOLIC CHANGES AND THE PATHOPHYSIOLOGY OF SPA**

Anabolic changes leading to syndesmophyte formation and ankylosis in SpA are of particular interest in understanding the pathophysiology of the disease. Current concepts suggest that, in patients with SpA, both mechanical triggers (enthesial stress) and inflammatory triggers (enthesitis) lead to mesenchymal tissue responses associated with the formation of new bone that bridges the intervertebral spaces, the small facet joints of the spine and the more, cortical bone changes in SpA do not represent bone loss and osteoporosis, because it would likely inhibit bone formation in general. Specific strategies to block periosteal bone formation without affecting trabecular bone remain to be determined. Such interventions need to be designed to specifically target pathways involved only in periosteal bone responses. The actual role of ankylosis and syndesmophyte formation in the clinical disease burden in SpA is still debatable. There is no doubt that advanced ankylosis contributes to impairment of spinal mobility and poor physical function. On the other hand, many disease symptoms of SpA seem to arise from inflammation rather than ankylosis. Thus, even patients with advanced ankylosis show clinical responses to TNF blockers. Because these agents do not influence ankylosis per se, the beneficial effects of TNF blockers in patients with SpA with advanced stages of ankylosis suggest that a substantial part of the disease burden in these patients is based on inflammation. Ambitious treatment responses such as “partial remission” according to the Assessment of Ankylosing Spondylitis (ASAS) definition are less frequently achieved in patients with advanced stages of ankylosis, whereas the extent of syndesmophyte formation does not affect standard clinical outcome measures such as the 40% response in ASAS criteria (ASAS40) and the Bath AS Disease Activity Index, 50% response (BASDAI50). These observations suggest that ankylosis attributes to some but by far not all the clinical symptoms of SpA and explain why effective control of inflammation without directly influencing syndesmophyte formation is rather effective in the treatment of SpA.

Nonetheless, prevention of ankylosis and structural bone changes in SpA seems to be an attractive treatment goal. If specific interference with periosteal responses without affecting the trabecular is not a feasible strategy, an alternative way to interfere with the process of ankylosis is to intervene early in the disease process before the periosteal response can start. Blocking inflammation early could thus prevent bony overgrowth in SpA. So far, however, studies in SpA have focused on longstanding disease, at a disease stage when molecular programs for periosteal responses have already been turned on. Animal data on bony spur formation suggest that an initial erosive phase is not required to achieve bone apposition and suggest that inflammation itself, with the likely addition of some mechanical triggers acting via the enthesis, initiate periosteal overgrowth.

**TREATMENT STRATEGIES**

The recent data on DKK-1 and sclerostin suggest that Wnt activation may be a decisive step in the formation of ankylosis in patients with SpA. Blocking of Wnt signals could thus represent an interesting strategy to inhibit ankylosis; however, this strategy bears the risk of generalized bone loss and osteoporosis, because it would likely inhibit bone formation in general. Specific strategies to block periosteal bone formation without affecting trabecular bone remain to be determined. Such interventions need to be designed to specifically target pathways involved only in periosteal bone responses. The actual role of ankylosis and syndesmophyte formation in the clinical disease burden in SpA is still debatable. There is no doubt that advanced ankylosis contributes to impairment of spinal mobility and poor physical function. On the other hand, many disease symptoms of SpA seem to arise from inflammation rather than ankylosis.

**CONCLUSION**

In summary, syndesmophytes in SpA are based on the differentiation of periosteal bone lining cells into osteoblasts leading to the deposition of new bone. This process, which results in ankylosis, is triggered by factors that support the differentiation of mesenchymal cells into osteoblasts. Prostaglandins such as prostaglandin E2. Wnt proteins and BMPs seem to be key signals, are responsible for bony overgrowth in SpA and constitute promising targets to halt structural changes in SpA.
REFERENCES


