Should We Consider Tumor Necrosis Factor as the Only Target in Spondyloarthritides?

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ABSTRACT. Understanding the biology of inflammation occurring at the entheseal-bone insertion has led to a better knowledge of the main drivers of inflammation in spondyloarthropathies. The clinical efficacy of tumor necrosis factor-α (TNF-α) blockers strongly supports the idea that TNF-α is a key molecule. Yet 40% of patients do not respond appropriately, indicating that other pathways are likely involved in these illnesses. Targeting T cells through a blockade of costimulating (CD28) molecules does not help, and in experimental models of sacroiliitis, targeting interleukin 6 (IL-6) did not provide any useful evidence. Immunohistological and functional data suggest that B cells, Th17, or IL-17A might be important, and indeed preliminary data concerning drugs targeting B cells and IL-17A seem to suggest clinical benefits. (J Rheumatol 2012;39 Suppl 89:94–6; doi:10.3899/jrheum.120255)

Key Indexing Terms: SPONDYLOARTHROPATHY TUMOR NECROSIS FACTOR-α Th17 INTERLEUKIN 17A DICKKOPF-1 WINGLESS SIGNALING PATHWAY

Over the last 20 years the greatest advance in treating spondyloarthropathies (SpA; ankylosing spondylitis above all) has been the introduction of tumor necrosis factor-α (TNF-α) blockers along with nonsteroidal antiinflammatory drugs (NSAID). In 1995 Braun, et al1 showed for the first time that TNF-α was expressed in the synovium of sacroiliac joints and could represent, as already shown in rheumatoid arthritis (RA), a therapeutic target in SpA. It was 5 years before the rheumatology community obtained the first clinical data on the benefits of a TNF-α blockade2 and 2 more years before randomized controlled trials could definitively show the clinical advantage over conventional treatment of using infliximab or etanercept3,4. TNF-α blockade has become a standard of care in treating SpA that is not responsive to an initial treatment with NSAID5.

It was also shown in RA that stopping TNF-α blockade was inevitably followed by a relapse. Yet in one such study, long periods of clinical remission could occur — it could take up to 45 weeks before relapse. This was a clear demonstration of therapeutic efficacy6 and thus this therapy became the mainstay of SpA treatment7. The supporting evidence is the demonstration that by targeting TNF-α, the bone marrow edema present in the subchondral bone at the sacroiliac joint level as well as at the vertebral bone in the spine and other sites promptly disappears when TNF-α is targeted through specific treatments8,9.

References


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BONE ACCRUAL, SYNDENSMOPHYES, AND RESIDUAL BONE MARROW EDEMA

Magnetic resonance imaging, especially techniques using either short-tau inversion recovery sequences10 or T1-post-gadolinium11, is best for assessing spinal inflammation and has become standard for the investigation of spinal and extraspinal bone marrow and entheseal-insertion inflammation. These images have demonstrated that syndesmophytes appear in areas of previous inflammation and that residual inflammation is the best biological explanation for bone formation. This is profoundly different from what we see in RA, in which the persistence of inflammation almost inevitably leads to subchondral bone erosion12. To determine why bone accrual can occur, it is necessary to consider that bone marrow–derived mesenchymal stem cells (MSC) can differentiate into adipocytes, chondrocytes, or osteoblasts. Data from several groups suggest that the wingless (Wnt/β)-catenin signaling family is central to osteoblast differentiation. Increased β-catenin is found in cells committed to the osteoblast lineage, and loss of β-catenin in osteoblast precursor cells results in reduced bone deposition. Dickkopf-1 (DKK-1), a soluble inhibitor of Wnt/β-catenin signaling, counteracts the Wnt-mediated effects on bone differentiation. Evidence from animal models and human studies supports an anabolic role for Wnt signaling in accrual and maintenance of bone mass, mediated by enhanced osteoblast differentiation/activity with concomitant suppression of osteoclast differentiation/activity.

Osteoblasts produce osteoprotegerin (OPG) and receptor activator of nuclear factor-κB (RANK) ligand (RANKL). RANKL binds to RANK and enhances osteoclast differentiation/activity. OPG, a soluble decoy receptor for RANKL, competitively inhibits RANKL/RANK interaction; therefore, it is the OPG:RANKL ratio that determines the net...
the TNF-α blockers (ASAS20/40/partial remission reached by α close to the clinical response rate of patients treated with 50 by 50%), the response seen in the TNF-naive group came Ankylosing Spondylitis Disease Activity Index (BASDAI) sional remission reached by 30/10/0%, respectively, and Bath Spondyloarthritis International Society (ASAS)20/40/partial remission reached by therapy, bone accrual is favored. This could explain why sites of previous bone marrow inflammation are those that present fat-bone appearance first and syndesmophyte formation afterward. Even more importantly, syndesmophytes develop in vertebral corners where inflammation had resolved more frequently than in those where inflammation persisted after anti-TNF treatment.

INTERLEUKIN 6, TGF-ß1, AND Th17
Recent histopathological data suggest that innate immunity is much more involved than adaptive immunity at sites of persistent inflammation. Initial immunohistological data showed that T and B cells are much more prevalent in sacroiliac joint biopsies more than are neutrophils, and that the same pattern of enriched CD68+ cells (macrophages) was seen in damaged hip tissue biopsies. In addition to the already well-known TNF role, it was seen that interleukin 6 (IL-6) was present in the early phases and that TGF-ß was present more frequently than IL-6 in the late phases of the illness. This could explain why SpA are characterized by persistent appositional new bone. While the histopathology could suggest a crucial role even of IL-6, experimental data do not support a definite role for IL-6 inhibition in SpA, and only clinical data on IL-6 inhibition will prove whether it adds to the existing strategies.

On the other hand, there is good evidence that immunohistology does not always provide complete information on the characteristics of the inflammation: B cells, which are thought to be mainly involved in autoantibody-positive autoimmune inflammation, are present, and targeting B cells has proven effective in patients naive to TNF blockers. In a formal trial, although there was no significant response by the TNF-failure group at Week 24 [Assessment of Spondyloarthritides International Society (ASAS)20/40/partial remission reached by 30/10/0%, respectively, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 by 50%], the response seen in the TNF-naive group came close to the clinical response rate of patients treated with TNF-α blockers (ASAS20/40/partial remission reached by 50/40/30%, respectively, and BASDAI50 by 50%). Rituximab (RTX) treatment not only resulted in a good clinical response, but C-reactive protein levels decreased significantly, especially in the TNF-naive patients with AS. The response to RTX started 4–8 weeks after the first RTX infusion and was sustained during treatment up to 24 weeks.

Targeting T cells through a blockade of the costimulatory axis (CD28) with abatacept did not provide evidence of clinical benefit in SpA, although it gave a clear demonstration of efficacy in peripheral psoriatic arthritis.

Biological data are strong regarding specific molecules of innate immunity that could determine the course of inflammation in SpA. Indeed, the most recent immunohistochernistry studies have revealed that IL-17-producing cells are abundantly expressed in zygapophyseal joints of SpA, while the presence of CD4+IL-17+ cells was similar in peripheral blood and synovial fluid of SpA and RA. IL-17A positivity was enriched either in myeloperoxidase-positive monocytes or in polymorphonuclear cells. IL-17A, more so than adaptive Th17 cells, could play a major role. However, the exact role of Th17 remains to be determined.

There is debate over whether Th17 cells are the main drivers of the transition phase from the innate to the chronic adaptive phase of immune inflammation or whether they are part of adaptive autoimmunity. Th17 cells are present in SpA as well as in RA, but also in recurrent microcrystal arthritides, either in blood or in synovial fluid, suggesting that they belong more to the transition phase than to the florid autoimmune chronic phase. According to these data, targeting IL-17 as well as Th17 could become a frequent therapy choice in the near future. Preliminary data suggest that blocking IL-17 can be clinically beneficial. Along this line, blockade of the IL-17/IL-23 axis might become part of the strategic therapeutic algorithm, because single-nucleotide polymorphisms of the IL-23R (receptor) gene seem to be significantly associated with SpA.

PERSPECTIVES
It appears clear that new therapeutic approaches are needed for the 40% of patients who are poor responders to TNF blockade. Reasons for TNF blockade unresponsiveness can only be determined through in-depth biological research on new pathogenetic pathways. Targeting IL-17A seems to be more promising than targeting IL-6. IL-17A (and IL-23, whose receptor gene polymorphism associates with SpA) could be the best approach, at least in the unresponsive subset of patients. In advanced disease, while targeting T cells through abatacept revealed an intrinsic weakness, targeting B cells was promising at least in patients naive to TNF-α blockers. This could suggest that TNF-α also maintains persistently activated B cells, or alternatively that B cells are major players that produce TNF or recruit TNF-α producing cells in the tissue milieu. All these data strongly reinforce the idea that a more advanced knowledge of the biology of the disease will improve SpA treatment algorithms.
REFERENCES