

ARE WE READY TO CHANGE THE PACE OF ARTHRITIS TREATMENT? TREATING PRE-ARTHRITIS AND VERY EARLY ARTHRITIS

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Rheumatoid arthritis (RA) is a prototype immune-mediated inflammatory disease, characterized by a symmetric polyarthritis usually involving the small joints of the hands and feet. Autoantibody positive RA is associated with more aggressive articular disease, higher frequency of extra-articular manifestations, and increased mortality. It has been estimated that 55–70% of RA patients have progressive disease resulting in joint destruction with as a consequence disability, loss of quality of life, reduced ability to work and increased health care utilization. RA is still associated with long-term morbidity and early mortality despite major developments in antirheumatic therapy. Among the connective tissue diseases RA is the commonest and the most important in socio-economic terms.

The past few years, research in the field of RA has focused on the earliest stages of disease, leading to the discovery that circulating auto-antibodies, increased acute phase reactants and asymptomatic synovitis^{1,2} precede the clinical onset of the disease. Before the onset of any signs of arthritis, elevated levels of auto-antibodies like IgM-rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) can be found in blood samples. These auto-antibodies may be present at a median of 5 years before clinical symptoms appear. Subjects with these auto-antibodies and arthralgia have a chance of 40–70% of developing RA within 5 years³.

Moreover, histological studies have shown all features of chronic synovial inflammation to be present in the earliest stages of the disease^{4,5}. Consistent with the notion that early arthritis represents chronic synovitis, a notable percentage of RA patients have signs of joint destruction at the time of initial diagnosis⁶. Taken together, these data form strong evidence that clinical signs and symptoms

may be preceded by a pre-clinical phase for several years and that early RA (as defined at present clinically) in fact represents chronic synovitis, although the duration of that presymptomatic synovitis has been unclear.

To determine whether the synovium is already affected during the earliest phases preceding clinical signs and symptoms of RA, we performed MRI and synovial biopsy in IgM-RF- and/or ACPA-positive individuals without a history of arthritis who were prospectively followed up⁷. The results show that the synovium is not abnormal during this stage, even in those who develop arthritis during follow-up. The presence of subclinical synovitis may probably last several weeks rather than months. Thus, systemic autoimmunity precedes the development of synovitis, suggesting that a 'second hit' is involved (Figure 1)⁷. This strengthens the rationale for exploring preventive strategies aimed at interfering with the humoral immune response before synovial inflammation develops. The individual and socioeconomic burden of this disease would support the development of preventive strategies. The outline of such a study aimed at in-

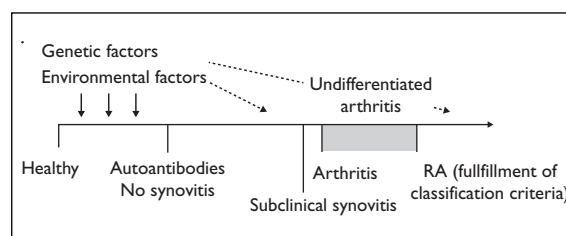


Figure 1. Timeline of autoantibody-positive rheumatoid arthritis (RA): the different stages of disease. Autoantibody formation may precede the development of clinical signs and symptoms of RA by several years. The presence of subclinical synovitis may probably last several weeks rather than months.

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terfering with the humoral response during the preclinical stage of RA will be discussed during this presentation at the Arthritis and Bone Symposium.

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