Uncoupling of disease activity and structural damage. Does it matter clinically?

Edith Villeneuve, Boulos Haraoui

Rheumatoid arthritis (RA) is an autoimmune disease characterised by synovial inflammation that can lead to joint damage through bone and cartilage destruction, loss of function and decreased quality of life. Fortunately, over the past few years, we have witnessed major advances in the management of RA with new agents and treatment strategies that have improved outcomes and made remission become a realistic goal. True remission has been defined as a state where there is no evidence of disease activity with complete resolution of signs and symptoms as well as arrest of joint damage and disability progression. Hence, inhibition of radiographic progression has become a major therapeutic goal given that patients on methotrexate alone and those who do progress, progress less than patients on methotrexate alone.2

This percentage increases up to 75–90% of lymphocytes present were monocytes which are at the beginning of the inflammatory cascade leading to the eradication of synovial inflammation. However, in order to explain this dissociation, Watson et al proposed a ‘two-compartment model’ with centres of pathology in both bone and synovium.11 Autoreactive B cells escape deletion in the bone marrow and migrate to either the synovium leading to synovitis or to subchondral bone where they will lead to osteitis and, eventually, bone erosion. Indeed, imaging studies have shown that the best predictor of radiographic progression is not MRI synovitis but bone marrow oedema which correlates with osteitis.12 Once initiated, it could be that the biologic processes occurring at each site are different with predominance for B cells in the bone, and possibly more T cells in the synovium explaining the effect of rituximab on damage even in patients without clinical improvement. Supporting this hypothesis, a study looking at the cellular components of bone oedema, known to be an important predictor of bone erosion, found that these were made predominantly of osteoclasts with a trend for more plasma cells and aggregates of B cells.13 On the opposite side, in a small study examining synovial tissue from five RA patients, 75–90% of lymphocytes present were identified as T cells.14 When comparing the cellular composition of bone marrow aggregates with synovial tissue, Jimenez-Boj and colleagues have also demonstrated...

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a higher number of B cells in the bone marrow aggregates and similar number of T cells.15

Finally, these novel findings are mainly interesting because of their clinical implications. As recommend by an expert task force, most rheumatologists now treat their patients to a target which should be remission or low disease activity.16 These recommendations, as well others developed by the different national organizations,17, 18 should definitely be implemented in all patients, especially those treated with methotrexate (MTX) or the traditional DMARDs, who display more radiographic damage despite good clinical control.19 However, results from this trial, and others with TNF inhibitors, suggest that this target may not have to be the same for patients on biologics than conventional DMARDs. We need to be more stringent for patients on methotrexate, while low disease activity may be adequate for disease on biologics since little structural damage will occur. There would also be less urgency to switch treatment in patients on biologics who are partial responders than if on methotrexate only. However, we should still aim at suppression of clinical symptoms as they are what affect patients most on a daily basis, and change treatment in patients with suboptimal clinical response despite the potential prevention of bone damage.

However, several issues remain: the majority of the recent clinical trials, including this one, have demonstrated very little radiographic progression.6, 20 Should we start using more sensitive techniques to evaluate structural damage, such as ultrasound, computerised tomography or MRI which will not only assess the structural damage but also residual inflammation in the synovium and bone that can lead to cartilage and bone lesions? Should these new imaging modalities be incorporated in the definition of remission? We would then need to define the threshold of imaging activity that will be clinically relevant.

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