Inflammation and ankylosis: still an enigmatic relationship in spondyloarthritis

Rik J U Lories,[1] Maxime Dougados[2]

The introduction of targeted therapies against cytokine tumour necrosis factor (TNF) alpha has dramatically changed the management, prognosis and perspectives of patients with ankylosing spondylitis (AS) and related forms of spondyloarthritis.[1] Both the soluble TNF receptor etanercept and the different anti-TNF antibodies are highly successful in reducing the signs and symptoms of disease, thereby improving quality of life, participation in the work force and the overall wellbeing of patients.[2 3] Clinical evidence suggests that anti-TNF therapies are more successful and the effect more sustained than in other diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease.[4] However, in contrast to what is seen in patients with RA, anti-TNF does not appear to have an impact on the structural progression of disease, a process characterised by ankylosis of the spine and sacroiliac joints in spondyloarthritis patients.[5–7] This aspect of the disease contrasts with the typical pattern of erosive joint destruction seen in patients with RA and with the associated protective effect of anti-TNF.[8]

Two hypotheses have been put forward to explain this clinical conundrum. The first hypothesis states that inflammation, including the upregulation of TNF, triggers local damage and subsequently repair leading to new bone formation and ankylosis, thereby establishing a causal coupling between inflammation and this process of ankylosis.[9] A decrease in inflammation may be necessary for repair to occur, with TNF acting as a brake on the specific mechanisms involved.[10] The second hypothesis states that a common trigger is responsible for both inflammation and new bone formation, but that both phenomena further develop in a largely molecularly independent way.[11] The question asked by these hypotheses is critical for the management of spondyloarthritis, because the former hypothesis would mean that early or preventive treatment with anti-TNF could have an effect on structural disease progression, whereas the latter suggests that the identification of a common but unknown trigger may lead to the development of new therapies.

In their paper published in this journal, van der Heijde et al[12] try to answer some of the lingering questions on the relationship between inflammation and the progression of ankylosis with a detailed study on MRI of inflammation in AS patients treated with the TNF inhibitor infliximab. Their data indicate that the presence of inflammation on the MRI in a vertebral unit (defined as the region between two virtual lines through the middle of each vertebra) marginally increases the likelihood of finding a new syndesmophyte in the same vertebral unit 2 years later but does not predict the growth of existing syndesmophytes. This observation may at first glance suggest coupling between inflammation and new bone formation, but on the other hand the majority of syndesmophytes developed in vertebral units that did not show any sign of inflammation on MRI at baseline. Therefore, the predictive value of MRI findings at the patient level was low. Obviously such vertebral units may have been affected by inflammation at any point in the 2-year study interval, but as the patients in the study were treated with infliximab, this appears rather unlikely. Nevertheless, there is a paucity of data on the week-to-week or month-to-month variability of MRI changes with or without arthritic treatment.

The data confirm earlier observations made in two smaller cohorts, which also implied that inflammation and new syndesmophytes at the same level were linked.[13 14] Together, these studies do not explain the lack of effect on radiographic structural disease progression suggested earlier over a 2-year period.[5–7] The link between inflammation and new bone formation does suggest that early treatment may have a preventive effect; however, syndesmophytes in this and other studies did not appear in sites where inflammation persisted. The number of such sites appears too small to draw final conclusions but the resolution of inflammation may be associated with syndesmophyte development.[15] On the other hand, neither this nor the other studies available can counterbalance the alternative view that inflammation and new bone formation may be independent phenomena with a common trigger: a positive MRI signal at baseline may just indicate active involvement of the site in the disease process and cannot establish a causal relationship between inflammation and syndesmophyte formation.

MRI and x-ray studies on disease activity and radiographic progression in AS pose significant challenges for clinical investigation.[16] Interreader variability may be high and this may affect the dataset and its analysis.[14 12] Moreover, different definitions of a positive MRI have been used among the studies, and a number of confounding factors may or may not be taken into account. Taking these specific limitations of the imaging studies into account, it becomes clear that the combined approaches including animal models, biomarker and imaging studies have failed to come up with a clear answer to the problem of inflammation and ankylosis. Data from mouse models have identified non-immune pathways such as bone morphogenetic protein and Wnt signalling as likely therapeutic targets for ankylosis,[17 18] and suggested that the inhibition of inflammation and joint erosion has no effect on ankylosis.[19–21] However, all these models have clear limitations and some caution is required when trying to translate the findings into human disease. Biomarker data also have limitations and recent evidence on the levels of DKK1 in patients with AS has suggested that complex regulatory mechanisms play a specific role.[18 22] In the clinical trial cohorts, one cannot exclude that the selection of specific patient subgroups eligible for the trial may have an impact on the structural outcome of disease. In this perspective, it remains noteworthy and too often overlooked that continuous treatment with celecoxib was successful in slowing down the structural progression of disease in AS patients.[23] Moreover, earlier work of Baraliakos and colleagues[24 25]

[1]Laboratory for Skeletal Development and Joint Disorders, Division of Rheumatology, Katholieke Universiteit Leuven, Leuven, Belgium
[2]Department of Rheumatology, Cochin Hospital, Université Paris-Descartes, Paris, France

Correspondence to Dr Rik Lories, Division of Rheumatology, UZ Leuven, Herestraat 49, B3000 Leuven, Belgium; rik.lories@uz.kuleuven.be

clearly demonstrated that the progression of ankylosis is a highly variable trait within the population of AS patients. Such a trait variability could be caused by environmental or acquired factors, but also by genetic factors. Despite the great progress in the last couple of years in our understanding of AS genetics,[26] the specific question as to whether the severity of ankylosis is a genetically determined outcome within the group of AS patients has not been answered. Alternative views on the onset of AS have been proposed, some of which are less known in the rheumatology community, such as a focus on muscle hypertonia and biomechanical stress rather than on inflammation.[27] Although largely unproved from the experimental point of view, these intriguing concepts provide some interesting ideas that could suggest that AS as defined in clinical practice is in fact the outcome of different initial processes all contributing to various degrees of inflammation and new bone formation.

Although probably controversial, this view on a broader spectrum of ankylosing disorders may lead to a better understanding of the disease processes and in the long term to better personalised medicine. There is a further need to define the impact of ankylosis on the individual patient and more specifically the smallest meaningful change in radiographic scores that has a functional consequence. In patients at high risk for progressive ankylosis, one may argue that continued non-steroidal anti-inflammatory drug treatment should be considered after potential side effects are taken into account.

Taken together, recent MRI studies on the structural progression of disease in spondyloarthritis and its relation to inflammation are another important step forward in our understanding of a disease that was neglected by most of the rheumatology research community for too long. The complex nature of the disease and the many factors that have recently been implicated in playing a role in its onset and progression indicate that further research is needed. The introduction of new criteria for the early diagnosis of axial spondyloarthritis is a great step forward from this perspective as it indicates that the clinical and research community is no longer constrained by a damage-defined definition of the disease but can adopt a more dynamic process identification approach.[28] [29] Further molecular understanding of the pathophysiology may in the next couple of years lead to better definitions of the disease and to

changes in management strategies. In this perspective, novel clinical and epidemiological data from cohorts with specific focus on early disease such as the German Spondyloarthritis Inception Chort, DESIR and esPAC projects will bring additional and specific insights into the disease course.[30–32]

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