

## REVIEW

## Structural integrity versus radiographic progression in rheumatoid arthritis

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**ABSTRACT**

Rheumatoid arthritis (RA) is a chronic, progressive and inflammatory disease often leading to irreversible destruction of articular structures and consequent disability. The key steps of RA pathogenetic mechanisms are the break of immune tolerance and the production of autoantibodies, followed by systemic and local inflammation resulting in damage of both subchondral bone (erosion) and cartilage (joint space narrowing (JSN)). Evidences from clinical trials suggest that erosions and JSN are the result of inter-related but partly independent pathogenetic pathways, in both cases mediated by pro-inflammatory cytokines, even if a direct effect of cyclic citrullinated peptides (anticitrullinated protein antibodies, ACPAs) on bone damage had been postulated. As a consequence, the suppression of inflammation provided by synthetic and biological disease-modifying antirheumatic drugs results in a decreased progression of bone and cartilage damage, supporting the effectiveness of the treat-to-target strategy. Nevertheless, radiographic progression may also be detected in patients achieving a sustained clinical remission. Two main reasons for this apparent uncoupling between clinical synovitis and damage progression should be considered. First, in some cases, the use of composite indices to define remission may not be completely adequate to identify residual disease activity, requiring the concomitant introduction of more sensible tools such as imaging. Second, the direct effect of biological drugs on bone destruction inducers, such as pro-inflammatory cytokines, may explain the suppression of radiographic progression despite the persistence of clinical synovitis. In this review, we discuss the link between autoimmunity, inflammation, joint damage and disability, focusing on how radiographic progression may predict functional disability.

be considered the most severe direct consequence of the disease; it is usually irreversible and causes permanent loss of function and subsequent disability.<sup>1</sup>

The key steps of RA pathogenetic mechanisms are briefly depicted in [figure 1](#). The break of immune tolerance is the first step towards autoimmunity, which arises as the production of antibodies specific for IgG (rheumatoid factors (RF)) or specific for cyclic citrullinated peptides (anticitrullinated protein antibodies, ACPAs), and usually precedes the clinically detectable onset of inflammatory arthritis.<sup>2</sup> The transition from the prearticular lymphoid phase to synovial inflammation is associated with the onset of clinical disease. Local inflammation is responsible for the progression of joint destruction by affecting the cartilage, ligaments or tendons, and subchondral bone. Finally, systemic inflammation, synovitis and structural damage may together contribute to the production of physical impairment and disability, which strongly impacts patients' quality of life. Research has elucidated some of the pathways of inflammation-induced articular tissue damage, leading to the development of novel therapies for the treatment of RA.<sup>3</sup> However, many pathogenetic mechanisms still remain not fully understood, underlining the need for further research in this area.

In this review about the mechanisms leading to joint involvement and disability, we will initially address the features of bone and cartilage damage in RA; subsequently, we will analyse the newest insights about the link between inflammation, autoimmunity and joint destruction, and between articular involvement and physical function impairment.

**INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory disease associated with articular, extra-articular and systemic effects. Disease severity varies considerably among patients according to several complex genetic and environmental factors. Depending on the level of disease activity, the destruction of articular structures in the course of RA may

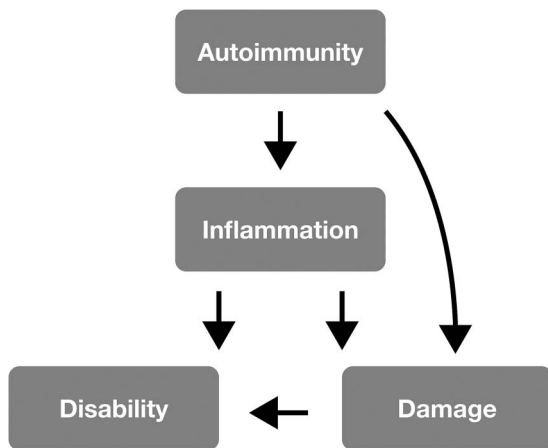
**JOINT DAMAGE IN RA: BONE VERSUS CARTILAGE INVOLVEMENT**

The detection and quantification of articular damage represent a major instrument for disease diagnosis, as well as for the monitoring and measurement of efficacy of drug



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**Figure 1** The rheumatoid arthritis pathogenetic paradigm.

therapy in slowing damage progression in patients with RA. Structural damage in RA typically affects both bone and cartilage, respectively, resulting in erosions and joint space narrowing (JSN). At present, radiography is widely used to assess RA damage in randomised clinical trials and daily clinical practice, even if several authors have reported that radiography has poor sensitivity in detecting joint damage components compared with MRI, CT and ultrasound (US).<sup>4 5</sup>

In all the currently used radiographic scoring methods (such as the Sharp method and its modifications), erosions and JSN are assessed separately and then aggregated into a total score, commonly used as the primary outcome in clinical trials and in clinical epidemiological research.

Pathogenetic mechanisms responsible for development of erosion and JSN in RA are well defined. Briefly, as to erosion, inflammation within synovial tissue induces osteoclastogenesis through increased expression of the receptor activator of nuclear factor  $\kappa$ -B ligand (RANKL) mediated by pro-inflammatory cytokines, such as the tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin 1 (IL-1) and IL-6. In addition, expression of Dickkopf-related protein 1 (Dkk-1) by synovial fibroblasts leads to inhibition of osteoblast differentiation and to production of sclerostin, which inhibits osteoblast activity. These two parallel processes result in increasing bone resorption and decreasing bone formation, leading to erosion formation.<sup>6</sup> Moving to cartilage degradation, the central event is the production of matrix-degrading enzymes such as aggrecanases (ADAMTS) and matrix metalloproteinases (MMPs) by both chondrocytes, induced by IL-1 and IL-17, and fibroblasts, stimulated by IL-1 and TNF $\alpha$ . Finally, chondrocyte death leads to the formation of empty lacunae and deprives cartilage from the ability to replenish the matrix.<sup>7 8</sup> Since the pathogenetic pathways mediating bone and cartilage damage involve different mechanisms and factors, one engaging question is if progression of erosions and JSN may be considered as the result of parallel events, or if these processes are separate in each individual joint. Data coming from a post hoc analysis of the ASPIRE trial, comparing

methotrexate (MTX) plus placebo with MTX plus infliximab in 870 patients with early RA, have clarified this issue.<sup>9</sup> Overall, erosions were the predominant type of damage observed at both baseline and after 54 weeks suggesting that, in the early phase of the disease, bone involvement is more frequent and more rapid than cartilage damage. Moreover, the presence of erosions in an individual joint was associated with a higher risk of erosion progression in that joint and, similarly, the presence of JSN in a particular joint predisposed to JSN progression in that joint, suggesting that the progression of existing damage is more frequent than the development of new damage. Overall, these data confirmed that, from a pathogenetic point of view, erosions and JSN are the result of inter-related but partly independent pathways.

Finally, data from long-term longitudinal cohorts have clearly demonstrated that radiographic progression in RA usually follows a linear or a sigmoid curve, but is more rapid in the first 2 years of the disease, with most of the damage occurring within 5 years.<sup>10</sup> As a consequence, the impact of both synthetic and biological disease-modifying antirheumatic drugs in slowing damage progression has been shown to be greater in MTX-naïve early RA compared with MTX-experienced late RA.<sup>11</sup>

#### FROM INFLAMMATION TO JOINT DAMAGE

The key role of pro-inflammatory cytokines in erosion and JSN formation supports the RA general paradigm that inflammation leads to structural damage. This concept has been demonstrated at both systemic and local levels by several reports. In a study conducted on 359 patients with RA, the persistence of systemic inflammation, expressed as the time-integrated C reactive protein (CRP) level, was able to predict both the progression of damage in already involved joints and the radiographic involvement of previously undamaged joints.<sup>12</sup> Moreover, data coming from the COBRA trial showed that local inflammation of an individual joint (expressed as swelling and tenderness scores) both at baseline and maintained during the 1-year follow-up period is a strong predictive factor of damage progression in that joint.<sup>13</sup>

Local inflammation has to be intended as both synovitis and osteitis (bone marrow as observed on MRI). It is still unclear whether subcortical bone involvement occurs as a consequence of cortical bone breaching which allows synovial access to the bone marrow, or whether osteitis necessarily or independently precedes erosion.<sup>14</sup> Anyway, it is conceivable that the RA prearticular phase begins in the bone marrow and subsequently involves the synovial membrane.<sup>2</sup>

An indirect evidence of the role of inflammation in damage progression is that suppression of inflammatory activity results in a decreased progression of both erosions and JSN. This effect has been clearly established for synthetic disease-modifying antirheumatic drugs (sDMARDs) such as MTX,<sup>15</sup> and biological DMARDs

such as TNF $\alpha$  inhibitors (TNFi), abatacept, rituximab and tocilizumab.<sup>11</sup> On the basis of this concept, the treat-to-target strategy for the management of RA indicated the abrogation of inflammation, identified in clinical remission or at least low disease activity (LDA), as the crucial step in preventing structural damage.<sup>16</sup> Indeed, several clinical trials confirmed that the application of treat-to-target and tight control strategies leads to better radiographic outcomes. In the FIN-RACo trial, radiographic progression during an 11-year follow-up period was significantly lower in patients who achieved a clinical remission at 1 year compared with patients who did not.<sup>17</sup> Similarly, the radiographic progression in patients with early RA treated with adalimumab during the second year of the PREMIER trial was strictly related to the additional time in remission during the first year, being the lowest for patients who maintained remission for at least 9 months, and the highest for those who maintained remission for only 3 months.<sup>18</sup>

However, several studies reported a significant radiographic progression also detected in patients achieving a stable clinical remission. Molenaar *et al.*<sup>19</sup> demonstrated that new erosion can occur in previously undamaged joints in about 15% of patients despite a persistent ACR clinical remission. Similarly, the radiographic progression in a French cohort of 191 patients with early RA was, as expected, significantly higher in patients not achieving a clinical remission, but can also be detected in one-third of patients who achieved a stable DAS44 score under 1.6.<sup>20</sup>

Two main reasons for this apparent uncoupling between clinical synovitis and damage progression should be considered. First, in a significant proportion of cases, clinical remission is simply not a true remission. The tool used in clinical practice to define the relationship between inflammation and joint damage is the measure of disease activity through composite indices such as Disease Activity Score 28 (DAS28), Simplified Disease Activity Index (SDAI) or Clinical Disease Activity Index (CDAI), which can be considered as surrogates of systemic and local inflammation. Agreement between these criteria sets was investigated in a non-randomised cohort of 1789 patients with RA from southern Sweden who were starting their first-course TNFi.<sup>21</sup> This study showed that disease activity states, according to the various indices, perform similarly at all levels, with the exception of clinical remission, which was significantly more frequent by using DAS28 (23%) compared with both SDAI (about 8%;  $k=0.42$ ) and CDAI (about 8%;  $k=0.40$ ). These findings suggest that radiographic progression encountered in patients achieving a DAS28 remission may be explained as the result of the application of a less stringent criterium for the definition of remission. As a consequence, in 2011, a EULAR/ACR task force redefined clinical remission criteria providing the currently used Boolean-based and SDAI-based more stringent definitions.<sup>22</sup> Nevertheless, data from the BRASS cohort recently demonstrated that even if joint damage is

significantly better predicted by SDAI remission than DAS-CRP remission, 12% of patients experienced a significant radiographic progression despite a stable SDAI clinical remission.<sup>23</sup> Some authors indicated the incorporation of imaging (in particular, MRI and US) in the criteria for the definition of remission as the solution for the apparent dissociation between clinical remission and continued structural deterioration in RA.<sup>24</sup> In fact, it has been demonstrated that both MRI and US have a significantly better sensitivity in detecting bone erosions compared with conventional radiography (68% and 42% vs 19%, respectively).<sup>25</sup> Moreover, the US power-Doppler signal or MRI bone oedema may be useful to identify active subclinical synovitis in at least 50% of patients achieving DAS28 clinical remission, as reported by Brown *et al.*<sup>26</sup> Recently, a systematic review of the literature confirmed the potential role of US power-Doppler signal positivity in predicting structural progression both at the patient level and at the individual joint level.<sup>27</sup>

Second, the link between inflammation and joint damage has been clearly demonstrated for sDMARDs such as MTX, but the introduction of biological drugs has partly changed this concept. The paradigmatic example is provided by the anti-RANKL antibody denosumab used to treat RA in a paper published by Cohen.<sup>28</sup> In this study, denosumab compared with MTX dramatically reduces the 6-month MRI erosion score progression, without any effect on the ACR clinical response, demonstrating that it is possible to completely stop bone damage without dampening inflammation. Something similar was also described with other biological drugs with different mechanisms of action. In a post hoc analysis of the ATTRACT trial, even in patients without clinical improvement, treatment with infliximab plus MTX provided significant benefit on radiographic progression, suggesting that disease activity and joint damage may be dissociated in patients treated with a TNFi.<sup>29</sup> This uncoupling has also been demonstrated in tocilizumab-treated patients coming from the LITHE trial. Considering only patients with high-moderate disease activity, radiographic progression in the tocilizumab-treated group was lower compared with MTX and similar to the groups in LDA remission.<sup>30</sup> On the basis of these data, it can be postulated that sDMARDs are able to slow damage progression only through the control of synovitis, whereas biological DMARDs may interfere with both synovitis and bone destruction inducers, such as pro-inflammatory cytokines and RANKL, explaining the uncoupling between clinical and radiographic response.<sup>6</sup>

### FROM AUTOIMMUNITY TO JOINT DAMAGE

Autoimmunity may produce joint damage through synovial inflammation, but a direct role of RA autoantibodies on bone damage beyond inflammation has also been postulated. In a very recently published study,<sup>31</sup> 242 patients with RA were evaluated in order to determine the additive effect of ACPAs and RF on the number and size of bone erosions detected by microCT.

Erosion size has been demonstrated as strictly related to both ACPAs and RF increasing titres, confirming that the concomitant presence of ACPAs and RF is associated with a higher erosive disease burden. However, very interestingly, RF influenced erosion size and number only in ACPA-positive patients but not in ACPA-negative patients, suggesting that ACPAs much more than RF may be crucial for bone damaging. To further demonstrate the crucial role of ACPAs, another study evaluated patients with preclinical RA comparing ACPAs-positive patients with ACPA-negative patients. ACPA-positive patients showed lower bone total volume, bone mineral density and cortical thickness, and more frequent cortical fenestration compared with controls.<sup>32</sup> From a pathogenetic point of view, these findings are well described in a review provided by Schett.<sup>6</sup> During the preclinical phase of RA, ACPAs are produced early by plasma cells and can stimulate osteoclast differentiation in the periarticular bone marrow by recognising citrullinated vimentin expressed on the surface of osteoclast precursor cells. Osteoclasts express high levels of the enzyme peptidyl-arginine deiminase type 2, which is induced by calcium flux and is responsible for protein citrullination. Induction of osteoclastogenesis leads to initial periarticular bone loss.

Anticarbamylated antibodies (anti-CarP) are another promising class of autoantibodies to characterise RA, especially in ACPA-negative patients. In a study conducted in 199 patients with RA, radiographic progression was significantly higher in anti-CarP-positive patients compared with negative ones, suggesting a possible role of anti-CarP in RA damage progression.<sup>33</sup>

## FROM JOINT DAMAGE TO DISABILITY

The prevention of articular impairment is a crucial step in order to prevent loss of physical function. Joint damage has been demonstrated to be a potential predictor of disability. In one study conducted over 10 years in 238 patients with RA with a relatively short disease duration (mean 2.3 years), a linear association between radiographic progression and Health Assessment Questionnaire (HAQ) score was observed. An increase of 10 units in the modified Sharp score was associated with a 0.03-unit worsening in HAQ score (total range 0–3 units).<sup>34</sup> However, the relationship between structural involvement and physical function seems to be deeply influenced by disease duration. In patients with early RA, inflammation and disease activity are predominant on joint damage in producing disability, with the potential for physical function improvement or reversal by effective treatment.<sup>35</sup> As the RA disease duration increases, joint damage reversibility progressively decreases and an increasingly large component of the loss of function is related to structural damage. In fact, in a cohort study involving 378 patients with early RA (duration <1 year), no association was found between damage progression and disability during the first 6 years of disease, first becoming evident only in late RA (disease

duration from 6 to 9 years).<sup>36</sup> By contrast, a longitudinal relationship between radiographic progression and HAQ score was observed from the beginning in a post hoc analysis of the TEMPO trial evaluating etanercept in a population of patients with established RA (mean disease duration 6.4 years).<sup>37</sup>

Aletaha *et al*<sup>38</sup> assessed the separate contributions of erosion and JSN in producing irreversible loss of function (measured by HAQ score) in a study conducted by pooling data coming from seven TNFi clinical trials (748 patients). In the crude analysis, both erosion and JSN seemed to increase with the increase in HAQ score. However, in the analysis adjusted for an average patient in terms of disease duration, age and disease activity, only JSN was still associated with HAQ, whereas erosions were not. Although the study was potentially affected by methodological limitations,<sup>39</sup> these data suggest that cartilage damage appears to be more clearly associated with irreversible physical disability than bone damage. However, a recent post hoc analysis of the BeSt study, evaluating the individual contribution of erosions and JSN in general and in four different joint groups in relation to physical disability in RA, found that erosions in the wrist were the only independent predictor of functional disability.<sup>40</sup>

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