Remission and radiographic progression in rheumatoid arthritis

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ABSTRACT

Complete remission, defined as the presence of clinical as well as radiographic remission, is the ultimate goal of treatment of rheumatoid arthritis (RA). Functional disability in patients with low disease activity is associated with joint inflammation and joint damage. Despite the methodologic problems of scoring radiographs, studies show that radiographic progression is an important outcome measure, and conventional radiography remains the best available method to assess it. Whether radiographic progression is entirely dependent on the presence of joint inflammation is a matter of debate; some evidence suggests that radiologic progression may continue in patients who appear clinically to be in remission. The potential availability of more effective drugs in the near future presents a need to further define and monitor progression of joint damage by more reliable methods. Better diagnosis of joint damage will assist in our quest to attain and document full remission in RA. Some newer techniques that provide direct assessments of metabolic activity in the inflamed joint appear to predict radiographic progression before it can be detected by conventional methods. Until these techniques are validated and assessed for predictive value, we would advocate that radiographic progression be added to existing criteria for clinical remission, in order to define remission in RA more comprehensively.

Introduction

Radiographic damage in patients with rheumatoid arthritis (RA) is one of the most important outcome measures in clinical trials and observational studies as well as in daily practice. Radiographic damage is regarded as resulting from previous inflammation of the joints and is correlated with functional disability at increasing levels over time. Joint inflammation may vary within the individual patient over time, as periods of active disease may alternate with periods of low disease activity or periods without any clinical joint inflammation, while radiographic damage is generally cumulative.

Whether radiographic progression is entirely dependent on the presence of joint inflammation is a matter of debate. In fact, knowledge about radiographic progression has largely been obtained in patients with high joint inflammation and may not reflect the same pattern in patients without joint inflammation, that is, those in clinical remission. If radiographic damage can progress in the absence of inflammation, that may have implications for the appropriate definition of remission, which is now based only on clinical symptoms.

This paper will focus on the relationship between functional disability and radiographic damage, and on long-term radiographic progression in patients with clinical remission. Furthermore, we will discuss briefly the possible relevance of including joint damage as a remission criterion and developments in the field of detecting joint damage.

Remission, functional disability, and radiographic damage

Functional disability is an important outcome in patients with RA. It results from joint inflammation and joint damage, among other factors (1, 2). In early disease, in general, functional disability is influenced primarily by joint inflammation (3), while in established disease, functional disability is also related to radiographic joint damage (2). To assess the relationship between functional disability, joint inflammation, and radiographic damage in a group of RA patients in remission, we performed a cross-sectional study in 186 patients (4). These patients had a median disease duration of 7 years, and 69% were rheumatoid factor–positive. All patients met modified American College of

Rheumatology (ACR) criteria of remission, which consisted of the original criteria except for fatigue (5); and 82% were clinically in remission according to European League Against Rheumatism (EULAR) remission criteria (6, 7), 92% having joint damage, with a median Sharp/van der Heijde damage score of 21 (interquartile range [IQR] 9-74). The median Health Assessment Questionnaire (HAQ) score was 0.25 (IQR 0-0.75), which is very low. Functional disability was independently correlated with pain, joint inflammation, radiographic joint damage, and disease duration in decreasing order of strength, but not to age, sex, and comorbidity.

These results illustrate that disease activity as well as radiographic damage may contribute to functional disability in patients with no or minimal disease activity, as also appears to be the case in patients with active RA (3). The implication of these findings is that, as in active RA, the goal of treatment in patients with low or inactive RA should be to both suppress joint inflammation to as low a level as possible and also to retard radiographic progression, in order to maintain functional capacity.

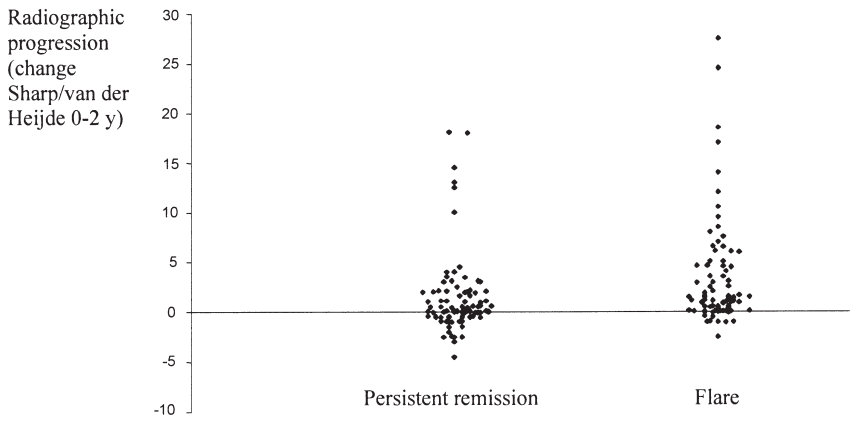

Fig. 1. Individual progression scores of RA patients with persistent clinical remission and those with a flare during 2-year follow-up (adapted from Molenaar *et al.* (5)).

Remission and radiographic progression

Radiographic progression is generally assessed by scoring radiographs of hands according to the Larsen method or by scoring radiographs of hands and feet according to the Sharp/van der Heijde method. Methodologic issues concerning assessing radiographs were reviewed in the 2005 supplement issue of *Clinical and Experimental Rheumatology* by Landewe *et al.* (8). The presence of measurement error complicates interpretation of whether radiographic changes (progression, remission, or healing of joints) occur, particularly in clinical trials in which only a relatively small proportion of patients have a significant progression. To appreciate the amount of radiographic progression at the individual level, Landewe *et al.* proposed to present radiographic data as cumulative probability plots, showing cumulative frequency distributions of radiographic scores from the lowest through the highest value in plots of every individual value of each treatment arm. However, the use of probability plots does not resolve the problem of measurement error, and more knowledge on how to define radiographic changes is needed, as more effective treatment regimens are becoming available.

Nevertheless, in a 2-year follow-up study we assessed the radiographic progression in 187 RA patients who were clinically in remission as defined by the modified ACR criteria of remission (5). Radiographs were assessed in random order by two trained observers, in line with recommendations proposed by others (9). Radiographic progression occurred, as expected, in the patients with a clinical flare during follow-up.

Interestingly, radiographic progression also occurred in patients who remained in clinical remission over 2 years and who had been clinically evaluated for persistent remission every 3 months. Progression was found more frequently in patients with flares compared to those with persistent remission, with Sharp/van der Heijde increases of >5 in 23% and 7%, respectively (Fig. 1). Similar differences were found when the EULAR definition and the original ACR definition of clinical remission were used (15% vs 6%, and 10% vs 7%, respectively). Likewise, the disease activity score (DAS) area under the curve (AUC) was higher in patients with relevant radiographic progression than in those with low or no progression (1.7 vs 1.3). DAS-AUC was a stronger predictor of radiographic progression than the absence of persistent remission. Furthermore, we found that persistent remission was reflected by a DAS-AUC of 1.6 or lower, suggesting that a cumulative DAS is more reliable for defining persistent remission, which is in line with observations made by others who also pointed out that remission criteria should be more stringent – that is, should include the following criteria: the absence of joint swelling and a prolonged period of remission (ie, >6 months) (10, 11).

We also analysed development of erosions in previously unaffected joints in patients who were in persistent remission for 2 years. Such erosions occurred in 14 patients, equally distributed between the first and the second year of follow-up. Although the limitations of clinical examination cannot exclude the possibility that some arthritis swelling may have been present, altogether our results indicate that radiographic progression does occur in RA patients who appear clinically to be in remission and suggest that radiographic progression may develop independently of joint inflammation.

The suggestion that radiographic progression may occur independently of joint inflammation is reinforced by several observations showing increased levels of bone markers in several clinical conditions. First, we have reported increased levels of urinary excretion of bone resorption markers, for example, pyridinoline, desoxypyridinoline, N-

terminal telopeptide (NTX), and C-terminal telopeptide (CTX) in patients with clinically inactive RA (12). Second, in another study we reported that CTX-2 levels correlate with radiographic progression in our RA patients in remission, independently of joint inflammation and disease duration (13). Furthermore, increased baseline levels of CTX-2 predict an increased risk of radiographic progression in patients with early RA treated with combination therapy (14). Also, the individual CTX-2 response after 3 months of therapy predicts long-term radiographic progression, independently of changes of disease activity (15). Third, the receptor activator of nuclear factor kappa B ligand (RANKL)/osteoprotegrin (OPG) ratio, a measure of osteoclast activation, is associated with long-term radiographic progression independently of joint inflammation (16).

To evaluate treatment efficacy, including radiographic progression, we currently are studying whether monitoring CTX-2 levels in addition to DAS in patients treated with combination therapy (salazopyrine, methotrexate, and prednisolone) can guide intensification of antirheumatic drug therapy, thereby improving outcomes.

Remission and joint imaging: magnetic resonance imaging, sonography, positron emission tomography

No radiographic progression need be present to fulfill the criteria for remission or complete clinical response as defined by the US Food and Drug Administration (FDA). Current guidelines for remission/complete clinical response specify that patients should meet ACR remission criteria and have radiographic arrest over a continuous 6-month period while not taking any antirheumatic drugs, or, in the case of complete clinical response, while continuing antirheumatic drug therapy (17). From a simplified clinical point of view, the absence of signs and symptoms of joint pain and joint swelling and normal acute phase reactant levels, as well as the absence of radiographic progression, are the minimum criteria for remission (11). However, it is known that patients without clinical signs of synovitis may have inflammation of the joints as evidenced by several other imaging techniques, including magnetic resonance imaging (MRI) (18) and ultrasonography (19). As outlined earlier, joint damage on conventional radiography follows synovitis after prolonged time. Therefore, achieving the ultimate goal of documented full remission appears to require not only effective drugs but also more definitive diagnostic techniques than monitoring disease activity by joint count and classical radiography (20, 21).

In contrast to conventional radiography, MRI has the advantage of a higher resolution, 3-dimensional imaging, and good soft-tissue contrast, thereby providing the possibility of detecting early abnormalities (synovitis, bone erosions and bone edema) and documenting changes in bone damage over a shorter time (18). As reviewed by Conaghan *et al*. promising results from MRI studies in RA show that early abnormalities may be detected that predict future radiographic lesions.

Large efforts are currently being made by the OMERACT-MRI-RA Working Group to assess the value of MRI in the evaluation of disease activity, including the presence of synovitis and joint damage. The objectives of this group include demonstrating adequate validity, discriminative power, and feasibility of MRI as an outcome measure (22).

The high resolution at the surface, low costs, and reproducibility of ultrasound give this imaging technique interesting potential for assessing joint inflammation in many joints and joint erosions in small joints (19, 23). To date, however, little is known about the validity and discriminative power of ultrasound as an outcome measure for RA.

Positron emission tomography (PET), a noninvasive imaging technique, has interesting potential since it has high sensitivity at the molecular level, in contrast to the detection of anatomic abnormalities with MRI, ultrasound, and conventional radiography. Additional advantages over ultrasound are the absence of depth limit, capability for 3-dimensional imaging, and the possibility of quantification. Furthermore, PET allows total body imaging, which is not feasible with the other imaging techniques such as ultrasound and MRI. PET in combination with computed tomography allows detection of abnormalities of bone as well as of molecular traffic. As such, PET may be an ideal tool to investigate the pathophysiologic processes involved in RA, inflammation, and joint destruction. In the past few years, 18-fluorodeoxyglucose (^{18}FDG) PET has been studied as a method to visualise synovitis by several groups (24-26). The activity of synovitis detected with ^{18}FDG-PET appears to be correlated well with structural changes detected by MRI and ultrasound (27). Recently, with dynamic [11C]-(R)-PK11195 PET, we observed specific imaging of macrophages in clinically active and in clinically nonactive joints of RA patients. Immunohistochemical analyses of synovial tissue were correlated very well with the tissue uptake as visualised by (11C)-(R)-PK11195 PET, suggesting that this technique may be useful to detect early synovitis, and eventually to monitor synovitis activity during treatment (28). Currently we are studying further the value of [11C]-(R)-PK11195 PET in assessing disease activity and predicting radiographic progression in RA patients who are clinically in remission.

Conclusion

Radiographic progression is an important outcome measure, which we would advocate should be added to criteria for clinical remission, to define remission in RA more strictly. Until now, conventional radiography has been the best method to assess radiographic progression, irrespective of the methodologic problems of scoring radiographs. The increasing availability of potentially effective drugs in the near future presents a more urgent need to define and monitor progression of joint damage by newer methods in order to attain and assess full remission in RA.

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