Clinical Implications of Understanding Radiographic Findings in Relation to Clinical Outcomes in Rheumatoid Arthritis

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ABSTRACT. The clinical progression of rheumatoid arthritis (RA) and longterm response to therapy is generally assessed by quantifying changes in joint space narrowing and erosions visible on serial plain radiographs. In patients treated with classic disease modifying antirheumatic drugs, the joint damage seen on radiographic images is usually directly associated with longterm functional disability. However, this relationship is not as clearly defined in patients treated with biologic agents. The apparent dissociation between clinical and radiologic outcomes in patients with RA who are treated with biologic therapies needs to be taken into consideration when evaluating the efficacy of treatment. (J Rheumatol 2009;36 Suppl 82: 11-16; doi:10.3899/jrheum.090125)

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The radiographic progression of rheumatoid arthritis (RA) and longterm response to therapy are generally assessed by quantifying changes in joint space narrowing and erosions visible on serial plain radiographs. Joint damage seen on radiographic images is associated with longterm functional disability. However, whether progression of radiographic damage over short periods is associated with immediate impairment in physical function is not known. This article explores new concepts in clinical and radiographic outcomes and their effects on clinical decision-making.

THE GOAL OF REMISSION

The main goal for the successful management of RA is remission, which is generally accepted to mean near-complete suppression of disease activity or an absence of discernible disease activity[1]. However, the concept of remission in RA has become increasingly complex. Clinical remission is generally defined as an absence of clinical synovitis or normal acute-phase reactants. Remission on imaging may require a lack of significant synovitis, not only on radiograph but also on sensitive imaging such as ultrasound and magnetic resonance imaging (MRI). In clinical practice, however, low disease activity and a lack of progression of structural damage may be accepted as true remission. Regardless of how it is defined, achieving remission is an important goal for patients with RA in order to prevent joint destruction, preserve adequate quality of life, and prevent disability. With the introduction of newer biologic therapies for the treatment of RA, this goal has become more realistic. However, failure rates remain high.

RADIOGRAPHIC OUTCOMES IN THE EARLY VERSUS LATE RA

The approach to radiographic assessment of RA is based on the effects of the disease on the appearance of articular structures. Progression of erosions and joint space narrowing has been shown to be most rapid during the early stages of RA, tapering slightly in later years[2]. In a prospective followup study of 147 patients with recent-onset RA[3], 70% of patients developed radiographic damage within 3 years of onset.

THE DISSOCIATION BETWEEN CLINICAL AND RADIOGRAPHIC OUTCOMES

Radiographic progression may occur in people who have satisfied the criteria for clinical remission, suggesting ongoing disease activity. One reason for this disparity is that current definitions of clinical remission, such as the Disease Activity Score (DAS)[4] and the American College of Rheumatology (ACR) criteria[5], allow for some residual disease activity. Patients may have up to 8 or 13 swollen joints, while still meeting the criteria for DAS28[6] or ACR remission, respectively.

Another reason for the dissociation between clinical and radiographic outcomes is that high-sensitivity imaging techniques may detect synovitis before clinical symptoms are present. In a prospective study in the United Kingdom[7], 96.2% of patients considered to be in complete clinical remission continued to have detectable synovitis on MRI. Synovial hypertrophy was detected by ultrasound in 73.3% of patients and by ultrasound with associated power Doppler flow in 43.3% of patients.

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Bone marrow edema was detected by MRI in 46.4% of patients.

In most cases, the physical examination is not sensitive enough to detect synovitis, which may account for some of the disparity between clinical and radiographic remission. In a prospective cohort study in The Netherlands, 187 patients with RA who were considered to be in clinical remission (according to modified ACR criteria) were followed clinically and radiologically for a period of 2 years[8]. Slight progression in radiographic abnormalities was observed among patients who remained in persistent clinical remission throughout the study period. Only 7% of patients had clinically relevant progression with clinical remission (Figure 1)[8]. This suggests that, when performed accurately, the physical examination is in most cases an adequate predictor of significant radiographic progression.

Just as radiographic progression is observed in patients with clinical remission, conversely, patients with clinical disease activity may have no evidence of radiographic progression. In the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT)[9], patients treated with infliximab who failed to achieve an ACR20 response still managed to improve significantly with respect to tender joint count, swollen joint count, scores on the Health Assessment Questionnaire (HAQ), patient global assessment scores, and C-reactive protein (CRP) levels. Therefore, an ACR response may not accurately reflect what occurs in individual core set measures. This concept was also demonstrated in patients treated with infliximab in combination with methotrexate (MTX) who failed to improve on these disease measures yet experienced minimal radiographic progression (Figure 2)[10]. These data suggest that the

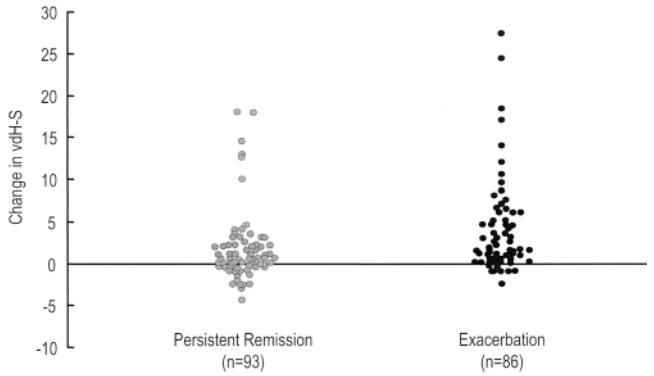

Figure 1. Radiographic progression, according to van der Heijde-modified Sharp score (vdH-S) among patients with RA in persistent clinical remission[8]. Reprinted from Arthritis Rheum 2004;50:36-42, with permission.

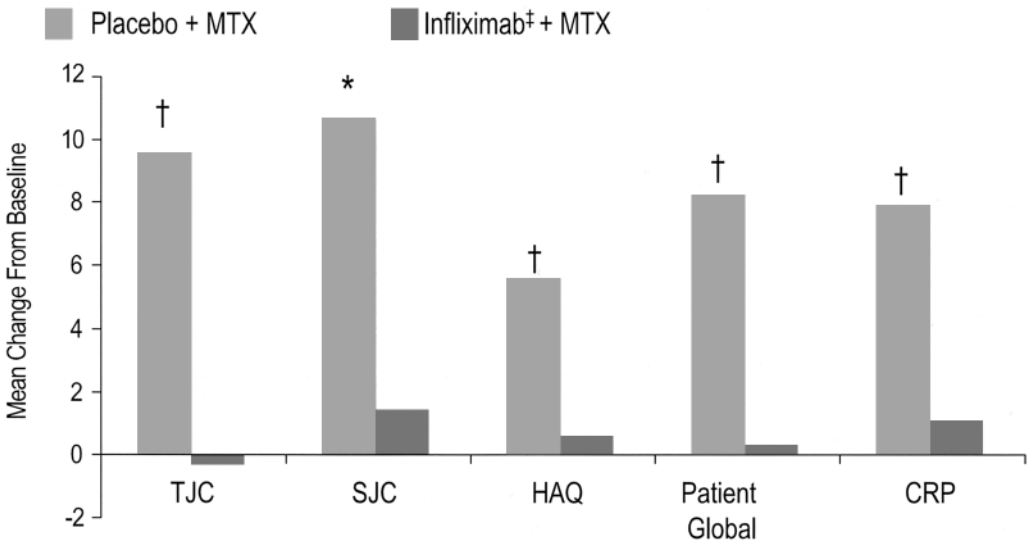

Figure 2. Mean changes in modified Sharp/van der Heijde scores among patients without improvement in disease measures, by treatment group (MTX plus placebo treatment; or infliximab plus MTX treatment)[10]. *$p < 0.01$ vs infliximab; †$p < 0.001$ vs infliximab; ‡infliximab 3 mg/kg or 10 mg/kg every 4 or 8 weeks. CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; SJC/TJC: swollen/tender joint count. Reprinted from Arthritis Rheum 2005;52:1020-30, with permission.

anti-TNF agents are able to impede joint destruction, even when clinical inflammation is not controlled.

The PREMIER Study further exemplifies the clinical/radiographic dissociation with anti-TNF agents. The trial compared a combination of adalimumab and MTX with each of the 2 drugs as monotherapy. Higher ACR responses were seen with the combination therapy than with either drug as monotherapy, but there was no significant difference between the 2 monotherapies in terms of ACR response. Unexpectedly, radiographic progression in the MTX-treated patients progressed to an even greater extent than the adalimumab-treated patients, as reflected in the mean changes in Sharp scores. However, it is important to note that mean changes in Sharp scores exclude patients who do not progress. These data then indicate that patients who progressed taking MTX did so to a greater extent than those who progressed taking adalimumab despite similar clinical responses. Cumulative probability plots were calculated to more readily identify the percentage of patients who progressed and the severity of their progression[12]. These data revealed that, overall, the majority of patients had a change in Total Sharp Scores (TSS) of 0 or less, and that the combination of MTX and adalimumab decreased both the number of patients with radiographic progression and the extent of progression in those patients. The cumulative probability plots also revealed that swollen joint counts appear to correlate more closely with radiographic progression than do tender joint counts. Patients with no tender joints were found to progress to a greater extent than patients with no swollen joints (Figure 3)[12]. Taken together, these studies indicate that the factors that cause inflammation are not the same factors that cause joint damage. As well, the majority of patients treated with an anti-TNF agent or high-dose MTX do not progress radiographically. Rather, mean changes in TSS seen in trials of anti-TNF agents and MTX appear to be influenced by a small subset of radiographic progressors. For the small subset of patients who do progress radiographically, the biologic therapies may prove to be particularly important.

In contrast to common thinking, radiographic remission is substantially easier to achieve than clinical remission. This has been highlighted in numerous trials, including the PREMIER trial[11] and the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE)[13], which indicate that a number of patients with active disease activity remain in radiographic remission. After one year of treatment, 50% of patients in the combination group had achieved clinical remission compared with 28% of the patients receiving MTX monotherapy ($p = 0.001$). Radiographic nonprogression was achieved by a higher percentage of patients

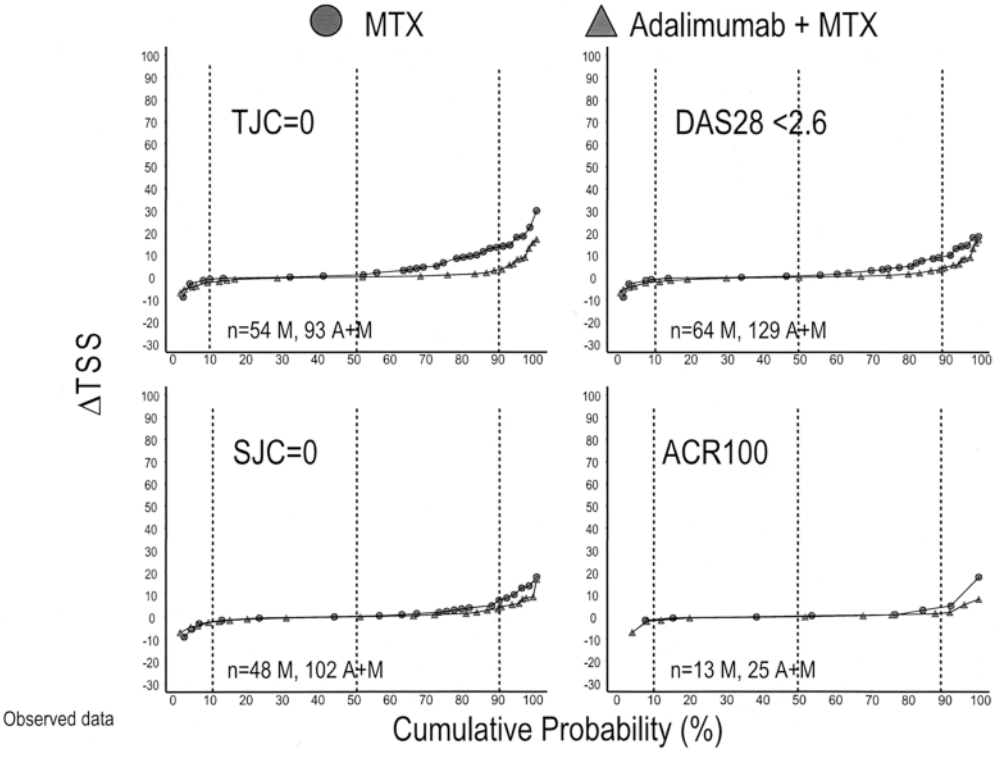

Figure 3. Cumulative probability plots of the change in total Sharp scores (ΔTSS) among patients in clinical remission in the PREMIER trial[12]. DAS28: Disease Activity Index 28; SJC: swollen joint count; TJC: tender joint count.

in both groups – 80% in the combination group and 59% in the MTX monotherapy group ($p < 0.001$)[14]. These results imply that a significant number of patients with clinical disease do not progress radiographically, particularly with the anti-TNF agents.

CLINICAL THERAPEUTIC TARGETS FOR MTX VERSUS ANTI-TNF AGENTS

In patients with RA who are treated with MTX, there is generally a good correlation between ACR scores and radiographic progression. The relationship between clinical targets and radiographic outcomes is not as straight-forward with the biologic therapies, where Sharp score progression tends to fall within the range of 2 points for every level of ACR response[15]. In the ASPIRE trial, when patients were treated with the combination of infliximab and MTX, even those patients with high levels of disease according to the Simple Disease Activity Index experienced a mean progression of only 2.1 points in the TSS[15]. The combination therapy also minimized Sharp score progression in relation to the number of swollen joints.

The message from these clinical trials is that therapeutic targets for the management of RA may not be the same for the biologic agents as they are for MTX. The anti-TNF agents are superior to MTX in preventing joint damage at every level of clinical response and disease activity state. Low disease activity may therefore be an adequate target for the patient who is in radiographic remission while undergoing treatment with a biologic therapy. In contrast, clinically detectable disease must be eliminated in patients treated with MTX monotherapy in order to control joint damage as effectively as the combination of MTX with an anti-TNF agent.

RADIOGRAPHIC EVIDENCE WITH THE NEWER BIOLOGIC AGENTS

Abatacept. The Abatacept in Inadequate Responders to MTX (AIM) trial compared the effects of the selective costimulation modulator abatacept with that of MTX monotherapy on radiographic progression of structural damage in patients with RA[16-18]. At one year, the reduction in change from baseline in Sharp scores was about 50% lower in patients treated with abatacept than in patients who received MTX monotherapy. This is lower than the 85% reductions generally observed with the anti-TNF agents[10,19]. However, in the open-label, longterm extension of AIM, the rate of progression in the original abatacept group was reduced by an additional 57% in Year 2 compared with Year 1[20]. Further significant inhibition was observed in Year 3 relative to Year 2 (Figure 4)[17]. Of note, the probability plot in the AIM trial shows that the combination of abatacept and MTX results in fewer patients with progression of structural damage (Figure 5)[17]. However, the degree of radiographic progression in this population of RA patients who failed to respond to MTX remained low in the group treated with MTX monotherapy. This suggests that MTX continues to protect against joint damage, even in the absence of a clinical effect. Whether these results would

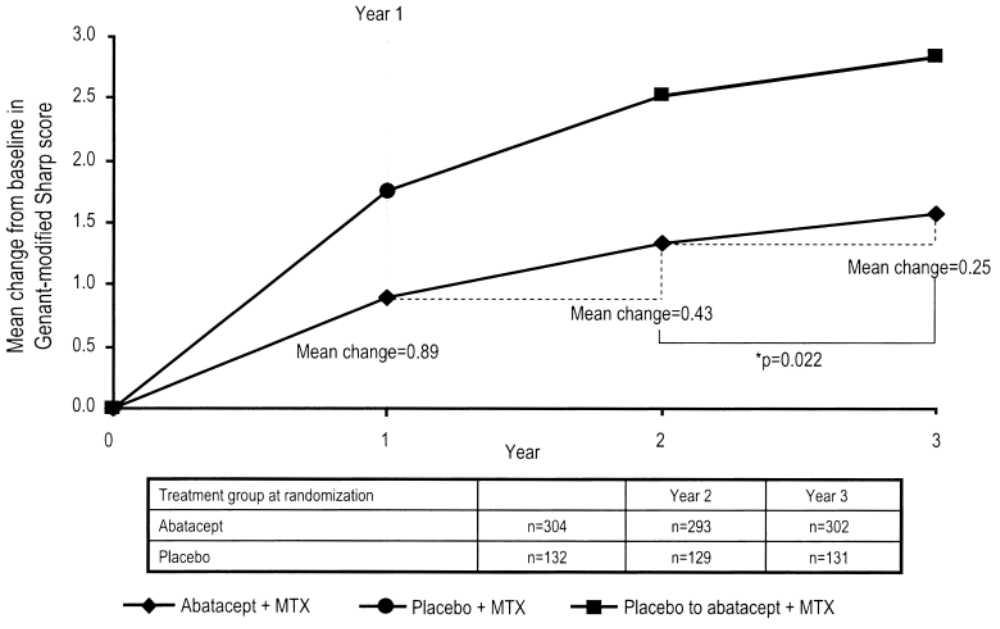

Figure 4. Increasing inhibition of structural damage progression with abatacept treatment over 3 years in the Abatacept in Inadequate Responders to Methotrexate (AIM) trial[17]. *Mean change in Year 3 relative to Year 2. All patients received a fixed dose of abatacept (~10 mg/kg) in the longterm extension of the trial.

be affected by changing the dose of MTX is a potential subject for future studies.

As with the anti-TNF agents, a dissociation between clinical and radiographic outcomes has been seen with abatacept. In the Abatacept study to Gauge Remission and joint damage progression in MTX-naïve patients with Early Erosive rheumatoid arthritis (AGREE), 509 patients with early RA (2 years' duration or less) and no previous exposure to MTX were randomly assigned to treatment with abatacept plus MTX or MTX monotherapy[21]. The co-primary endpoints were remission, defined as DAS28 < 2.6, and nonradiographic progression, defined as a change in TSS of 0 or less. At one year, 41.4% of patients treated with the combination of abatacept and MTX had achieved clinical remission, compared with 23.3% in the group receiving MTX monotherapy. As in the COMET trial[14] with the anti-TNF agent etanercept, a higher percentage of patients achieved radiographic nonprogression than achieved clinical remission; 61% of patients treated with the combination of abatacept and MTX achieved radiographic nonprogression, compared with 53% of patients treated with MTX monotherapy.

In AGREE, the mean change in TSS at one year was significantly less for patients treated with the combination of abatacept and MTX (0.63) than for patients treated with MTX monotherapy (1.06; p = 0.040).

Rituximab. The Randomized Evaluation of Longterm Efficacy of Rituximab in RA (REFLEX) study investigated the effects of rituximab in combination with MTX on joint structural damage in comparison with MTX monotherapy in 457 patients with RA who had experienced inadequate response to one or more anti-TNF agents[22]. At one year, marked improvements in radiographic outcomes were seen in patients treated with rituximab, including a significantly lower mean change in total Genant-modified Sharp score (p = 0.0043), erosion score (p = 0.0106), and joint space narrowing score (p = 0.0007) compared with the group treated with MTX alone. Similar to the results with abatacept seen in the AIM trial, the reduction in change from baseline in Sharp scores was about 50% in patients treated with rituximab compared with patients who received MTX monotherapy. However, a key difference with the REFLEX trial is that 80% of patients in the control group were given rituximab as a rescue agent, which would influence the difference between the active and control groups. Another key difference is that REFLEX is the only trial to examine the efficacy of a biologic agent in RA patients who have failed an anti-TNF agent. As with the anti-TNF agents, a dissociation between clinical and radiographic responses was seen in patients treated with rituximab. While the group who received MTX monotherapy showed a linear progression of Sharp score changes with an increased swollen joint count, patients treated with rituximab experienced minimal Sharp score changes, regardless of their swollen joint count.

CONCLUSIONS

Disease activity in RA results in radiographic damage; however, this relationship is often dissociated in patients who are treated with a biologic agent, both at the patient level and at the level of the individual joint. Maximal

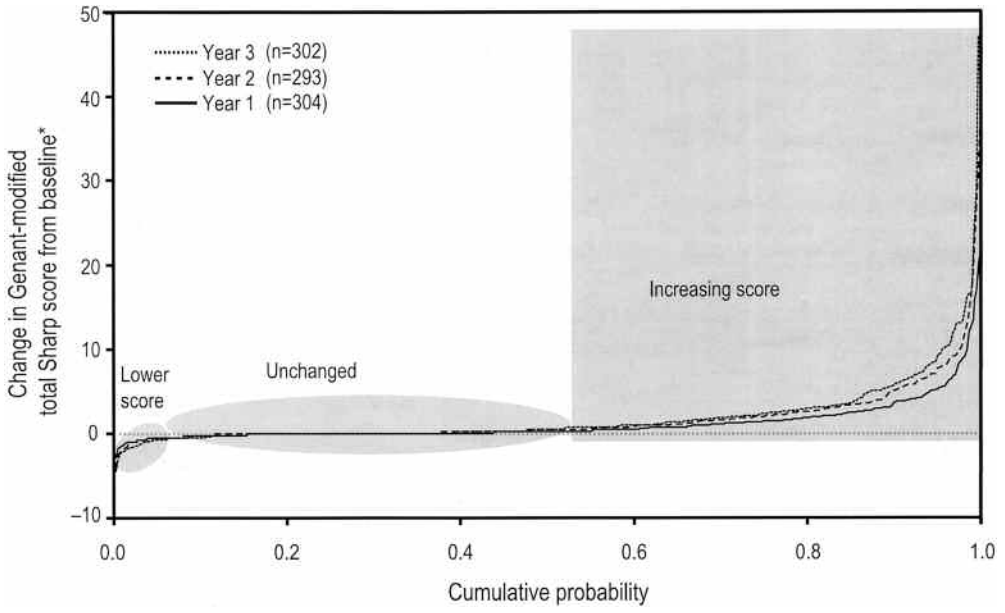

Figure 5. Distribution of changes in the Genant-modified total Sharp score in patients originally treated with abatacept in the Abatacept in Inadequate Responders to Methotrexate (AIM) trial[17]. *Change of zero or less in the Genant-modified total Sharp score from baseline.

reduction of synovitis is necessary to prevent disease-related side effects for patients treated with conventional therapy such as MTX. Clinical remission combined with an absence of radiographic progression may be the only adequate goal for the management of RA. The dissociation between inflammation and radiographic progression in patients undergoing treatment with a biologic agent may allow the option of continuing treatment if clinical disease activity cannot be otherwise reduced, as long as it is acceptable to the patient, and no radiographic progression is present.

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