Rheumatoid Arthritis Joint Progression in Sustained Remission Is Determined by Disease Activity Levels Preceding the Period of Radiographic Assessment

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Objective. Joint damage is related to disease activity in rheumatoid arthritis (RA), but the degree of its progression and the temporal associations between disease activity and joint damage are unclear. The aim of this study was to evaluate whether there is a latency in the effect of disease activity on radiographic progression in patients with RA.

Methods. Data were obtained from the PREMIER trial, a 2-year randomized, controlled clinical trial of adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in early RA. Radiographic progression of joint damage was calculated using the modified total Sharp score in a subset of patients whose disease was in remission (Simplified Disease Activity Index < 3.3) in the second year of the trial. The progression of damage in the second year was compared between groups of patients whose disease was already in remission for an additional period of 3, 6, or 9 months during the first year. Analysis of variance was used to test for a linear trend.

Results. Among 794 patients with early RA, 119 (15%) achieved sustained remission during the second year, with no difference in radiographic progression across the 3 treatment groups. Radiographic progression in the second year was significantly different between patients with 3, 6, or 9 additional months of remission during year 1 (mean change in the modified Sharp score 1.19 in those with 3 additional months of remission versus 0.20 in those with 6 additional months of remission and −0.32 in those with 9 additional months of remission; P < 0.05). The results were supported by similar findings in a series of sensitivity analyses.

Conclusion. These data indicate that the level of disease activity as well as the duration of remission affect subsequent progression of radiographic damage in RA. This latency between disease activity and its effects on radiographic progression should be considered when evaluating radiographic outcomes in trials of RA.

Joint destruction is the major hallmark of rheumatoid arthritis (RA) (1) and is usually evaluated by radiographic imaging (2,3). It constitutes the irreversible component of the RA disease process (4), accumulating with time and leading to increasing disability (5–8). Thus, joint damage is associated with bad outcomes in RA (5,8,9).

Several risk factors have been linked with joint destruction (1,9–11), and it is unequivocally recognized that joint damage increases with increasing disease activity (6,7,11–16). However, progression of joint destruction is not always directly coupled to the signs and symptoms of RA, since, with the advent of tumor necrosis factor (TNF) inhibitors, it has been noted that joint damage can be retarded or stopped even if active disease prevails (17,18). Nevertheless, because joint

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destruction is a clear sequela of disease activity, it can be stated, in relation to the outcomes of any therapy, that only the induction of remission can reliably halt disease progression, and therefore this outcome should be a goal in the treatment of RA.

However, there have been recent reports that joint damage can accrue even in states of remission (19,20), and several reasons for this finding have been discussed. However, a question not sufficiently addressed is whether there is a lag time until the consequences of disease activity can be visualized as joint damage on conventional radiographs, since resolution of inflammation may not necessarily mean immediate halting of the destructive process.

In the majority of RA patients, joint damage becomes visible after ~1–2 years of disease (21,22), long after the occurrence of signs and symptoms of synovitis. Moreover, in experimental models of destructive arthritis, synovitis and clinical symptoms precede the occurrence of histologic joint erosions, although osteoclasts, the pivotal cell population involved in bony damage, are activated even earlier (23). Thus, the evolution of joint destruction may require the prolonged presence of inflammatory cytokines. Vice versa, halting of progressive disease activity may require a prolonged absence of mediators of inflammation.

In the present study, we evaluated the possibility that disease activity levels before a baseline radiograph is obtained might influence the progression of radiographic damage that will become visible on a subsequent radiograph. To investigate the presence of such a “carryover” effect of disease activity on joint damage, we used a large clinical trial database of patients with early RA who were treated with methotrexate (MTX) monotherapy, adalimumab monotherapy, or the combination of adalimumab plus MTX (24), with a 2-year followup of disease activity and radiographic assessments.

PATIENTS AND METHODS

Source data. We used data from the PREMIER trial, a multicenter, randomized, double-blind, controlled, phase III clinical trial comparing adalimumab (40 mg every other week), MTX (mean dosage 16.9 mg weekly), and the combination of adalimumab and MTX in patients with early RA who had not been previously treated with MTX (24). For the present study, we were provided data on all patients enrolled in the trial. A central institutional review board or independent ethics committee at each participating site had approved the study, and all patients had provided written informed consent.

Patients enrolled in the PREMIER trial were required to be at least 18 years of age, to have been given the diagnosis of RA (25) within 3 years before the trial start, and to have had no prior treatment with MTX. In addition, patients had to be either positive for rheumatoid factor or have erosions in at least 1 joint on radiographic assessment. In addition, patients were required to have active disease at the start of the study, defined as ≥8 swollen joints, ≥10 tender joints, and an erythrocyte sedimentation rate (ESR) of ≥28 mm/hour or a C-reactive protein (CRP) concentration of ≥1.5 mg/dl.

Outcome measures. Using the source data, which included the swollen joint count (SJC), the tender joint count (TJC), patient’s and evaluator’s global assessments of disease activity (PGA and EGA, respectively) on a visual analog scale (in cm), and the ESR or CRP level (26), we were able to calculate the Simplified Disease Activity Index (SDAI) (sum of the SJC + TJC + PGA + EGA) was used for validation purposes (14,27). In addition to the CDAI, the Disease Activity Score in 28 joints using the CRP level (DAS28-CRP), calculated as (0.56 × √TJC28 + 0.28 × √SJC28) + (0.36 × log10(CRP + 1)) + (0.014 × global health) + 0.96, which is based on the traditional DAS28 (30), was used for validation purposes. The disease activity states of remission and low, moderate, or high disease activity have previously been defined on the basis of all of these scoring systems (26). In the SDAI, the respective cutoff values for remission, low disease activity, moderate disease activity, and high disease activity are scores of ≤3.3, >3.3–11, >11–26, and >26, respectively (31).

Radiographs were obtained at baseline, year 1, and year 2. Four readers with no knowledge of the treatment allocations were used for this study, with 2 of these readers reviewing the radiographs of each patient and assessing joint erosions (on a scale of 0–5) and joint space narrowing (on a scale of 0–4), using the modified total Sharp score (2). The readers were blinded to the sequence of the radiographic images. Only patients with complete clinical followup data at baseline, 3, 6, 9, 12, 15, 18, 21, and 24 months, as well as total Sharp scores available from all 3 radiographic assessments, were evaluated in this post hoc analysis of the trial.

Statistical analysis. In the initial analysis of the data, we identified the degree of radiographic progression during the second year of the PREMIER study for patients with different disease activity levels in the second year. We therefore used the area under the disease activity curve (AUC) of the SDAI in the second year of the study (based on the radiographic assessments every 3 months), and adjudicated patients to groups according to defined disease activity levels, with those in remission having an SDAI-AUC of ≤3.3, those with low disease activity having an SDAI-AUC >3.3 to ≤11, those with moderate disease activity having an SDAI-AUC >11 to ≤26, and those with high disease activity having an SDAI-AUC >26. We performed these analyses separately for the adalimumab, MTX, and adalimumab plus MTX groups.

Based on the observations in previous studies (32), we expected that patients whose disease was in sustained remission, irrespective of therapy, would have no radiographic progression, and that there would be no difference between
the 3 treatment groups in this regard. Therefore, we pooled the 3 treatment arms to address the questions on the effects of sustained remission on radiographic progression. To this end, we selected only the subgroup of patients who had an SDAI-AUC ≤ 3.3 during the second year of the study. In this subgroup of patients whose disease was in remission in the second year, we then analyzed the effect of disease activity levels during the first year on radiographic progression during the second year. Graphically, the results are depicted as bar charts to compare mean progression, and we used probability plots to compare the distribution of individual patients. Parametric methods (analysis of variance [ANOVA] with testing for a linear trend component) were used to compare radiographic progression between the 3 groups.

The impact of disease activity in the first year on progression of joint damage in the second year was assessed by evaluating whether the duration of remission prior to the visit at month 12 was relevant. For this purpose, all patients whose disease was in remission in year 2 were used. Similar to the definition of year 2 remission, year 1 remission was again defined based on the SDAI-AUC, i.e., the respective period of year 1 during which the time-integrated SDAI did not exceed 3.3. We thus compared 3 groups of patients according to the additional number of months in remission in year 1, as follows: 1) patients whose disease was already in remission from month 9 to month 12 (3 additional months in remission), 2) patients whose disease was in remission from month 6 to month 12 (6 additional months in remission), and 3) patients whose disease was in remission from month 3 to month 12 (9 additional months in remission). An analysis of 0–12 months was not performed, because disease activity was high for all patients at the baseline visit, given the inclusion criteria, and therefore no patient would be ascertainable for such a group.

To test the robustness of the results, we performed additional analyses with modified parameters. In one sensitivity analysis, we defined the disease activity categories based on other disease activity indices, the CDAI and the DAS28. We also investigated whether the trend observed in the pooled group would be present if analyses were done separately in the MTX, adalimumab, and adalimumab plus MTX groups. Finally, to further support the concept of a carry-over effect, we investigated the year 2 progression in 3 patient groups based on 3 tertiles of average disease activity during year 1 (defined as the bottom, middle, or top tertile on the basis of the SDAI-AUC from month 3 to month 12).

*P* values less than 0.05 were considered significant. All analyses were performed using the SAS package, version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Patients. In the PREMIER trial, 799 patients were randomized to receive treatment, of whom 268 were in the adalimumab plus MTX combination group, 257 were in the MTX monotherapy group, and 274 were in the adalimumab monotherapy group. Of these, 794 patients had complete radiographic data at baseline, year 1, and year 2. For the analyses on radiographic progression in the second year, 501 patients had complete data on SDAI scores available (190 in the combination group, 158 in the MTX group, and 153 in the adalimumab group). Because the numbers of missing data items were different depending on the scoring system, the numbers of patients with complete data varied when the CDAI or DAS28-CRP was used to assess disease activity levels, particularly in the main analysis that focused on the subgroups with different duration of remission in year 1. Therefore, the demographics and clinical characteristics of the different subsets of patients are not presented herein, but these data can be obtained from the previously published report on all patients studied in the PREMIER trial (24). In our study, the characteristics of the patients in the subgroups did not differ across the 3 treatment groups (results not shown).
Radiographic progression in different disease activity states. Among the group of patients whose disease was in sustained remission as defined by the SDAI during the second year of the study, the extent of radiographic progression was similar in all 3 treatment groups (mean change in the modified total Sharp score 0.05 in the MTX group, 0.13 in the adalimumab group, and −0.14 in the adalimumab plus MTX group). Moreover, the mean radiographic progression did not significantly differ from 0, as indicated by the standard errors of the mean for each treatment group of patients whose disease was in sustained remission (Figure 1). This halt of progression was not seen in patients in any other disease activity state, although patients who received treatment with adalimumab in combination with MTX generally showed less radiographic progression compared with those in either the MTX monotherapy or the adalimumab monotherapy group.

Similar results were obtained when disease activity states were defined using the CDAI or the DAS28-CRP, although, on the basis of the higher stringency of the SDAI and CDAI (29,31,33), more patients were considered to have disease in remission and fewer were grouped in the low disease activity state when categorized by the DAS-CRP than when categorized by the SDAI or CDAI. Consequently, radiographic progression of joint damage in patients considered to have disease in remission according to the DAS28-CRP was numerically higher in the MTX monotherapy group as compared with the other 2 treatment groups (results not shown). As reported previously in patients receiving other TNF inhibitors (17,18), the combination of adalimumab plus MTX retarded progression of joint damage at all disease activity levels and virtually halted it in those categorized to the low disease activity state (Figure 1). Based on the fact that there was essentially no radiographic progression in the group of patients whose disease was in SDAI-defined remission in any of the 3 therapy groups (Figure 1), which is consistent with previous results from a similar study (17), we pooled the 3 treatment groups for further analyses of joint damage progression in patients whose disease was in remission.

Carry-over effect of previous disease activity. Among the 794 patients with early RA, 119 (15%) (29 in the MTX group, 66 in the adalimumab plus MTX group, and 24 in the adalimumab group) had achieved a disease activity level of sustained remission according to the SDAI throughout months 12–24. In these patients, the mean ± SEM progression of the modified total Sharp score during year 1 was 1.0 ± 2.8.

To address a possible carry-over effect into year 2, we investigated whether the duration of remission during the first year influenced the levels of radiographic progression during the second year. As shown in Figures A and B, the duration of remission in year 1 significantly affected the levels of radiographic progression in year 2.
2A and B, the low level of radiographic progression seen in patients considered to have disease in sustained remission throughout the second year further decreased with an increase in the period of remission during the first year (\(P = 0.008\) between groups). B, the Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) \((n = 130\) for 9 additional months in remission, \(n = 33\) for 6 additional months, and \(n = 16\) for 3 additional months) \((P\) not significant [NS] between groups), or C, an approach defining the average levels of disease activity during the first year as tertiles of the area under the SDAI curve \((n = 40\) in the bottom tertile, \(n = 41\) in the middle tertile, and \(n = 40\) in the top tertile) \((P\) NS between tertiles). In addition, data from the main analysis using the SDAI to define remission were analyzed by subgroups according to the individual treatment arms of D, methotrexate monotherapy \((n = 13\) for 9 additional months in remission, \(n = 8\) for 6 additional months, and \(n = 2\) for 3 additional months) \((P = 0.014\) between groups), E, combination of adalimumab and methotrexate \((n = 29\) for 9 additional months in remission, \(n = 11\) for 6 additional months, and \(n = 9\) for 3 additional months) \((0.1 > P > 0.05)\), and F, adalimumab monotherapy \((n = 10\) for 9 additional months in remission, \(n = 3\) for 6 additional months, and \(n = 3\) for 3 additional months) \((P\) NS between groups).

The average disease activity between month 12 and month 24, which, if it had been dissimilar, could have accounted for differences in the radiographic progression rate, was similar between the 3 groups of patients whose disease had additional time in remission during year 1 \((\text{mean SDAI} 1.8, 1.5, \text{and} 1.4\) in those with 3, 6, and 9 additional months of remission in year 1, respectively; \(P\) not significant). Thus, these data indicate that carry-over effects governed the differences in the progression rates among patients whose disease was in remission.

Validation of main results using different definitions. We validated the results from the main analysis of the average disease activity during the first year in a series of additional analyses. When we used the CDAI instead of the SDAI to assess disease activity states, and...
thus eliminated the potential influence of the CRP level, results similar to those observed using the SDAI were obtained in the 3 groups of patients whose disease had additional time in remission according to the CDAI (Figure 3A). Likewise, when using the DAS28-CRP definition of remission (Figure 3B), a similar trend was found among the 3 groups.

Furthermore, when the effect of average disease activity according to the SDAI during year 1 was analyzed with the use of tertiles of average disease activity from month 3 to month 12 (using the SDAI-AUC), similar patterns were observed; namely, patients in the lowest tertile of year 1 disease activity had less progression during the second year compared with those in the second and third tertiles (Figure 3C), although all of these patients had disease in remission during year 2.

Finally, similar effects were also present within the individual treatment groups, i.e., the MTX monotherapy group (Figure 3D), the adalimumab plus MTX group (Figure 3E), and the adalimumab monotherapy group (Figure 3F). Although these individual treatment group analyses were stratified, and the numbers remaining in each of the subgroups were very small, the results taken together support the initial finding that the achievement of a state of remission and the duration of that state, rather than the type of therapy, were responsible for the halt of radiographic progression.

**DISCUSSION**

In this post hoc analysis of data from the PREMIER trial, we addressed the question of whether joint damage can be generally arrested in states of sustained remission. This has not been resolved hitherto, because progression of radiographic changes is known to be associated with disease activity; however, several reports have indicated that joint destruction can progress even in patients who achieve longer-term remission (19, 20, 34). To address this issue, we evaluated the scores of radiographic progression at baseline, year 1, and year 2 in patients from the PREMIER study.

Given the high disease activity in all patients at entry into the PREMIER study, and considering the period of time necessary to reduce or halt disease activity even under the most favorable circumstances, an evaluation of radiographic changes during the first year would have provided only limited insights, since the initial period in active disease may already have driven joint damage. Analyzing changes in radiographic scores in the second year using the year 1 radiographs as a baseline measure, however, ensured that at the time of the year 1 radiographs, disease in many patients had already reached low activity or remission. Stringent criteria for sustained remission were applied by using the remission definition of the SDAI and by requiring that remission was sustained throughout the period analyzed.

Although there was a virtual arrest of progression of radiographic scores at the group level in patients who maintained remission between month 12 and month 24, some patients in all 3 treatment groups who showed progression of radiographic scores despite being in clinical remission throughout the second year, as depicted in the probability plots in Figure 2B. When we analyzed whether expanding the duration of remission into the first treatment year would have an effect on radiographic changes in the second year, we found that, indeed, a proportion of patients in whom joint damage progressed during the second year had attained their state of remission only shortly, i.e., ≤3 months, before the year 1 radiograph was obtained. This also translated into progression of radiographic scores at the group level. In contrast, in 80% of patients who had already achieved remission for 9 months before the first radiograph was assessed, joint destruction did not progress, and in the remainder of patients, maximal progression was numerically lower than that in those with shorter periods of remission. Therefore, joint damage in RA does not progress in states of sustained remission in the majority of patients. However, to fully confirm this fact, remission has to be present for a prolonged period of time before the first radiograph is obtained. Thus, we were able to show that preceding disease activity is a relevant determinant for radiographic progression between 2 time points.

Several explanations for this finding could be considered. One explanation would be that disease activity was misclassified and, rather than remission, low disease activity prevailed during the observation period, at least in some patients. However, this is unlikely, since among patients receiving MTX monotherapy, joint damage was halted only in those whose disease was in longstanding remission; if remission had been misclassified in these patients, the halt in progression would not have occurred, given their progression of joint damage during low disease activity. It might, however, be the case that subclinical joint inflammation prevails for an additional period of time after clinical remission has been achieved (20), leading to smouldering progression of damage; in this case, the lag time observed in our study would be overestimated.

As another explanation, joint damage could be an event that is totally separate from inflammation, at least in
a subset of RA patients. However, this would not explain the results presented, particularly the difference between shorter- and longer-term remission. Moreover, in light of the compelling information on the effects of cytokines involved in RA pathogenesis (35–37) as well as the association of disease activity with joint damage in RA, it is unlikely that induction of joint destruction can be completely separated from the processes of inflammation.

Yet another explanation for our findings could be methodologic in nature, in that joint damage may need a certain amount of time to become visible by radiographic assessment. Indirect evidence for this hypothesis stems from data obtained using other imaging techniques, especially magnetic resonance imaging (MRI). Several authors have suggested that joint damage can be seen much earlier by MRI than radiologically (20,38). Thus, any identification of joint damage in the course of remission would be the consequence of such a lag period in detection.

Finally, our findings could be related to the biology of joint destruction. In an experimental model of arthritis, joint damage identified by histology did not concur with the development of osteoclasts, since the evolution of erosions takes more time (23); this has also been observed in clinical practice (21,22). Conversely, stopping the function of osteoclasts, once they have been activated, may require a longer time than would the reversal of inflammation. Regardless of the underlying mechanism, our finding of reduced joint damage progression in patients with lower disease activity before the baseline radiograph was assessed supports the hypothesis that joint destruction, at least as detected by traditional radiographs, is subject to a carry-over effect.

In summary, sustained remission is associated with a halt of joint damage irrespective of the type of therapy. The shorter the period of remission, the more likely some mild progression may be found, and this is likely a consequence of a carry-over effect of past periods of inflammation. Thus, sustained remission is the ultimate goal to prevent the occurrence of joint destruction and, consequently, the accrual of irreversible disability in RA. Moreover, in the process of therapeutic decision-making, the assessment of radiographic progression of joint damage will have to account for these observations regarding the latency of radiographic manifestations in patients with RA.

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We dedicate this manuscript to our dear friend and esteemed colleague Dr. John Sharp, who recently passed away, and to Dr. Sharp’s family. Dr. Sharp’s spirit will continue to enrich our scientific work.

AUTHOR CONTRIBUTIONS

Dr. Aletaha had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Aletaha, Smolen.

Acquisition of data. Sharp, Segurado.

Analysis and interpretation of data. Aletaha, Funovits, Breedveld, Smolen.


Statistical analysis. Aletaha, Funovits.

REFERENCES


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Erratum

In the article by Keystone et al in the November 2008 issue of *Arthritis & Rheumatism* (pages 3319–3329), there was an error in the data on serious adverse events leading to death in the group treated with certolizumab pegol 400 mg plus methotrexate. The incidence rate per 100 patient-years was correctly shown as 1.3; however, the actual number of deaths should have been listed as 4.

We regret the error.