

Radiographic Progression in Rheumatoid Arthritis: Does It Still Happen and Does It Matter?



Radiographic progression (RP) has been an important objective outcome for assessing the comparative efficacy of therapies in clinical trials. It is being increasingly reported in observational studies of clinical care. RP is typically reported as a change in a modified version of the Sharp score (SS)¹. Reported rates and extent of RP are much lower in patients with rheumatoid arthritis (RA) treated intensively, to a target of low disease activity or remission while receiving disease-modifying antirheumatic drugs (DMARD), including more effective doses of methotrexate (MTX)². However, persisting swelling of ≥ 2 (of 28) joints is associated with further RP (defined as a change > 0.5 over 1 year) using SS scoring methods³. RP continues throughout the course of RA⁴, although less often for patients who are in remission more often⁵. RP reporting varies widely, using different cutoffs such as the smallest detectable change (SDC) to describe “rapid radiographic progression” (RRP)⁶. Thus rates of RP will vary depending on study design, patients studied, disease activity, and intensity of treatment interventions.

In this issue of *The Journal*, Ørnbjerg, *et al* publish additional results from the Danish Biologics Registry (DANBIO) on the rate and extent of RP in patients with serial hand radiographs using tumor necrosis factor (TNF) inhibitor (TNFi) therapy over an average of 1.5 years⁷. Ørnbjerg, *et al* aimed to understand the effect on RP of drug switching and withdrawal. Prior analyses had shown that the extent and rate of RP dropped significantly once patients failing DMARD switched to TNFi therapy⁸. DANBIO patients had longstanding disease of 9 years, higher than usual rates of smoking (38%), high C-reactive protein (CRP) levels for DMARD and steroid-treated patients, and 82% in this study had erosive disease. Patients had failed up to 6 DMARD (mean of 2.2), and started a TNFi [infliximab (IFX; 59%), etanercept (ETN; 18%), adalimumab (ADA; 23%)]; 80% continued to take MTX (median dose 15 mg/weekly) but 60% still needed steroids, though in lower doses. The SS increased (by > 0) in 29% who were

classified as having RP, though over the study course this was on average only 1 point, mostly a new erosion. Only 4% had RRP defined as a change beyond twice the standard error or SDC.

Biologic switching was common, occurring in 30% of patients. Most switched to a second TNFi. Of those receiving initial IFX, ETN, and ADA (33%, 20%, and 27%, respectively), switches were due either to loss of effect (in 52%, 42%, and 39%, respectively) or adverse events (36%, 42%, 30%). Of those receiving TNFi monotherapy, fewer patients continued IFX (31%) compared to ETN (73%) and ADA (50%). Only 10% withdrew biologic therapy (reasons were not provided). Importantly, there was more RP in patients who switched or withdrew from biological therapy during this study. They had an independent greater risk for RP (OR 1.68 and 2.06, respectively, $p < 0.001$); however, it was not noted whether progressors had higher rates of disease activity. Not surprisingly, patients who continued biologic therapy throughout the study period — even if they had switched — had a 50% lower odds of progression than those who withdrew TNFi.

Baseline factors associated with a risk for damage included rheumatoid factor (RF) positivity, high CRP, advanced age, and steroid use over the prior 2 years. Others have shown a relationship between RP, RF, and CRP⁹, but this is considered the first time that use of steroid was an independent predictor for RP.

So what does one make of these results? It is reassuring that RP is minimal once patients failing DMARD are treated with TNFi. Few had RP of concern. However, damage occurs more often if patients need to switch TNFi, possibly because of ongoing active synovitis. This study did not report whether switchers were TNFi nonresponders, TNFi nonadherent, or never achieved remission. Authors had previously reported that persistent disease activity is the main reason for ongoing structural damage¹⁰ and that remission rates were low in this registry¹¹. Older age, low functional status, and concomitant prednisolone treatment

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were negative predictors of clinical response and remission. It was previously reported that patients treated with IFX had lower rates of treatment response, disease remission, and interestingly, lower drug adherence. ADA-treated patients had the highest rates of treatment response and remission, and ETN-treated patients had the longest drug survival rates.

The finding that biologic therapy is protective of damage in clinical practice was also observed in the Swiss registry¹², where a combination of achieving remission even once and taking biologics was most protective for damage. It may be possible to infer that more damage occurred in DANBIO because patients did not achieve remission as rapidly, because initial CRP elevations were associated with further damage.

Did these authors overclassify RP? This was an observational study performed as part of practice. Obtaining correctly positioned hand films may not always have been possible, causing more variability in SS. For randomized controlled trials (RCT), a change from 0 is considered reportable¹³. However, others suggest classification of RP in studies should be based on an increase in the SS at least beyond the SDC^{6,14,15}. Thus, the surprisingly high rates of progression seen in DANBIO, albeit small in absolute change, may have been within the margin of error. Likely the authors chose this SS cutoff to classify RP to interpret findings in light of prior RCT of TNFi therapy. The authors specifically highlight that only 4% of patients were classified as “rapid progressors” defined using the SDC criterion. The main message from this and similar studies is that most patients taking TNFi therapies in settings of usual care are likely to be well protected from significant radiographic damage, as would have been predicted from clinical trials.

As is seen in other observational studies, use of glucocorticoids is a predictor for poor outcomes. Possibly the need for patients to persist with steroids is a surrogate marker for poor prognosis because these patients are also less likely to achieve sustained remission¹⁶. Interestingly, the Danish guidelines for biologic use include the continuous need for > 7.5 mg prednisolone per day as an indication for biological treatment. In a recent analysis of ESPOIR, a study of patients with early RA, 40% were using steroids in the third year, and only 13% were taking biologics. Very little disease progression occurred as long as patients were in remission according to the Simplified Disease Activity Index or the Clinical Disease Activity Index. Again, in this study there was slightly more RP in those patients taking DMARD compared to those receiving biologics¹⁷.

In the DANBIO study, the initial damage level was an independent predictor of further damage, even in this population of high biologic users. This again suggests that efforts to use therapies to stringently control disease early and to reduce overall burden of synovitis should lower the risk of RP.

This study reported only slightly less RP than would be expected based on TNFi RCT. A systematic review examining RP over 1 year based on SS in TNFi-treated patients from RCT noted increases in SS ranging from 1.1–2.8 in studies published after 2002¹⁸. Only the ASPIRE trial¹⁹ had very high rates of progression. In MTX-naïve patients treated with TNFi in RCT, RP was only slightly higher, ranging from 1.37–5.70¹⁸. It is quite possible that the degree of RP reported in DANBIO could easily have fallen in this range because DANBIO scores were based only on hand radiographs and did not include radiographic changes in the feet. This may have resulted in an underestimate of erosiveness because others have shown that failing to add scores from serial foot radiographs can result in missing up to 30% of additional erosive disease²⁰.

Putting aside issues of adjudication of damage progression, let us consider the more important question: Why should health providers continue to be concerned about halting damage? The reason is simple. Less damage is associated with better function. Bombardier, *et al* summarized the literature on the relationship between RP and function²¹. Of 23 studies addressing this question, almost all showed a statistically significant relationship between worsening damage and decline in function. This relationship was strongest in the more methodologically sound studies. More importantly, Navarro-Compán, *et al* have clearly demonstrated that functional disturbances as assessed using hand function questions from the Arthritis Impact Measure Questionnaire are clearly affected by damage progression²². Thus, it remains imperative for rheumatologists to be certain that their patients with RA are not damaging their joints. The ongoing use of glucocorticoids seems insufficient to protect joints and could be an indicator to consider biologic therapy. Intensification of treatment to achieve very low levels of disease activity should continue to be a priority in aiming to prevent RP. However, when that is not possible, patients are far less likely to have significant RP when using TNFi.

VIVIAN P. BYKERK, MD,

Department of Rheumatology,
Hospital for Special Surgery,
535 East 70th St.,
New York, New York 10021, USA

Address correspondence to Dr. Bykerk. E-mail: bykerkv@hss.edu

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