

Rheumatoid Arthritis: Are Current Research-based Guidelines Clinically Relevant?



In this issue of *The Journal*, Ciobotariu, *et al*¹ examine joint damage and progression in patients with rheumatoid arthritis during clinical remission. They report less erosion progression in patients receiving biologic disease-modifying antirheumatic drugs (DMARD) compared to nonbiologic DMARD (nbDMARD). In addition, scores on the Health Assessment Questionnaire-Disability Index (HAQ-DI), a secondary outcome of disability, were better for patients taking biologics than for those taking nbDMARD. Despite the statistically significant differences noted, the changes were very small and one might wish to consider whether statistical differences translate into clinically relevant ones.

First, there are issues with the meaning of small changes in radiological progress. Second, there are more basic issues regarding the pathogenetic meaning when radiographs do not change.

The minimal clinically important difference in radiographic progression is variable depending on the methods used, ranging from 2.3–5.5 units using the Larsen vs the Sharp/van der Heijde methods². With changes of only 0.9 (adjusted data) in the biologic DMARD and 1.37 in the nbDMARD groups over 3 years in radiographic progression, it is clear that the differences are far below this number. Even if one assumes a linear change per year (not at all guaranteed), this means that using a difference in the rate of erosion of 0.4 units per year, one would need a minimum of 6–13 years of therapy to reach even a minimal clinically significant difference between treatments, radiographically. If not radiographically different, does this study posit a clinically significant functional difference between therapies? Given that the minimal clinically significant change in HAQ-DI is at least 0.22 (and is often considered to be 0.4), combined therapy would still have to continue for 3–5 years (given that the HAQ-DI difference noted was –0.1 vs –0.18 in the 2 groups — a difference of 0.08) to separate the 2 regimens in a functionally meaningful way. Thus, this article seems to be pointing to a very small and probably not clinically meaningful difference between therapies. It is true, of course, that the literature supports Ciobotariu, *et al*'s conclusion, so their article could be considered supportive of that contention, even if weakly so.

The pathogenetic meaning of radiographic change should

also be considered. Historically, the cessation of radiographic progression has been used as 1 definition of disease remission, because that cessation is thought to reflect little or no inflammation. The lack of radiographic progression, then, could be a surrogate for lack of clinical progression or preservation of function over the longer term. However, a number of studies concluded that radiologic progression continues despite attaining clinical remission, regardless of the criteria used to define this remission^{3,4}. Additionally, the timepoint at which radiographic progression is examined appears to be significant. Aletaha, *et al* reported that the level and duration of particular disease activity (in this case, remission) are important determinants for radiographic progression⁵. Therefore, the point at which a radiograph is obtained is key to determining remission. This raises questions about whether radiological progression using observational data over such a limited period (as the observational trial under consideration) is really useful, either in clinical trials or in clinical practice.

Ultrasound, magnetic resonance imaging (MRI) techniques, and positron emission tomography scans, as well as the introduction of single photon emission-computed tomography scans, may allow greater in-depth evaluation of the joint space, including the inflammatory or preclinical component of bone damage⁶. These techniques are not yet fully validated nor are their predictive values yet defined, relative to standard radiographic films⁷. However, given that such validation will occur, with increased ability to detect subclinical disease and inflammation, we again raise the question as to the utility of radiologic remission.

Are there, then, other ways to reconcile the lack of radiographic progression with a clinical measure of remission, thus restoring the value of plain radiographs to clinical trials? A score of < 2.6 on the 28-joint Disease Activity Scale (DAS28)⁸ has been widely used as a measure of remission and it could be compared to radiographic progression. However, many if not most investigators admit that DAS28 < 2.6 often represents low disease activity rather than true clinical remission. Clinical Disease Activity Index (CDAI) < 2.8 and simplified Disease Activity Index (SDAI) < 3.3 and the “Boolean American College of Rheumatology/European League Against Rheumatism” criteria of remission are all far more stringent criteria of

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remission and should be correlated with radiographic change (or lack thereof). Some investigators argue that given their stringent formulae, these criteria (especially the Boolean) occur so infrequently that they offer limited application outside clinical trials settings⁹. In a recent study by Svensson, *et al*¹⁰, DAS28 identified more patients in sustained remission than did either SDAI or the Boolean criteria. Hence, it was proposed as the preferred tool in longterm observational studies, although the lack of correlation with longterm outcomes considerably weakens such an argument.

The issue of the meaning of remission, then, remains open. Logic would dictate that those definitions (CDAI, SDAI, Boolean) that completely abrogate inflammation are more likely to reflect true remission and would correlate with better longterm outcome, and thus are more appropriate for correlation with imaging such as radiographs. None of these measures were used in Ciubotariu, *et al*'s article¹, unfortunately, thus not furthering either their argument or the larger argument about the most appropriate measure for remission. Alternatively, one would consider the use of outcomes of disability as a measure of clinical remission. If one were to agree to this, one then would debate whether a self-reported measure such as HAQ-DI should be used. One may argue that HAQ-DI correlates well with disease activity. Saleem, *et al*¹¹, pointed out that ultrasound power Doppler signaling as well as HAQ-DI were independently associated with risk of a flare when studying patients who were in remission. However, structural limitation is bound to have ceiling effects, in which very high HAQ-DI and/or modified total Sharp score reach an upper plateau. That is exactly what was seen by Tanaka, *et al*¹². Other factors, which would limit the use of HAQ-DI or other functional measures, are comorbid conditions, and could confound correlations¹³. An example could be severe heart failure, where even complete RA remission would not improve function in a person who is nearly bedridden.

Ciubotariu, *et al*¹ raise questions about the meaning of remission, and as noted, do not really answer them. However, their article remains very useful in bringing these issues to the forefront: (1) how much change in a measure is needed to be clinically rather than statistically relevant; (2) which measures of clinical remission are relevant; and (3) what is the meaning of radiographic remission in an era of other more sensitive imaging of inflammation?

Those questions, in turn, raise these points: (1) is seeking remission (by an agreed measure and an agreed amount) relevant? Both Ciubotariu, *et al*'s and our answer is "yes"; (2) is remission attainable? Both Ciubotariu, *et al* and we would say "yes" although our definitions and requirements are different; and (3) are the definitions realistic? Ciubotariu, *et al*¹ would say yes and we would only say yes if one used other definitions (more stringent), other imaging techniques (e.g., MRI or ultrasound), and another study design (e.g., a longer study or a more responsive population of patients).

SUZANNE KAJAJA, MD,

Clinical Instructor;

DANIEL E. FURST, MD,

Carl M. Pearson Professor of Rheumatology,
Director of Therapeutic Research,
Department of Rheumatology,
David Geffen School of Medicine,
University of California at Los Angeles,
1000 Veteran Ave., Room 32-59,
Los Angeles, California 90095-1670, USA.

Address correspondence to Dr. Furst. E-mail: defurst@mednet.ucla.edu

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