The measure of our measures

Attempts to quantify various aspects of rheumatoid arthritis (RA) go back at least as far as the first half of the last century [1]. The importance of separating ‘disease activity’ from function and structural damage became increasingly clear especially with the advent of new disease-modifying anti-rheumatic drugs (DMARDs) and biological agents and the need to assess their efficacy in clinical trials. The question as to which measures of disease activity one should select is a vexing one. Should it be joint tenderness or pain, morning stiffness, joint swelling, range of movement, function? Should extra-articular manifestations such as fatigue be included? Should one add laboratory values such as the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP)? Should such measures be reported separately, or should summation be attempted? The last question was particularly important since therapeutic trials frequently reported multiple outcomes of uncertain relative importance, often differing from outcomes reported in other trials. There have been several attempts to devise an instrument which would measure the overall activity of RA. Lansbury was one of the first to introduce a summary ‘activity index’ which incorporated morning stiffness, fatigue, the amount of aspirin used, grip strength, a count of painful/tender (but not swollen) joints, and the ESR [2]. The Lansbury index was criticized for some statistical shortcomings in therapeutic trials, and different instruments were suggested, such as the ‘pooled index’ conceived by Smythe et al. [3]. Whatever its statistical merits, that index also included measures which are either subjective or depend on patient cooperation, such as grip strength, morning stiffness, functional assessment and number of tender or painful joints [3]. The two best known and most commonly used summation measures for activity of RA are the Disease Activity Score (DAS) and the American College of Rheumatology preliminary core set of disease activity measures, often referred to as the ACR20 (meaning that a 20% improvement was sought or achieved) [4, 5]. The DAS has been further modified to the DAS28 to indicate that only 28 specified joints are assessed for pain/tenderness and swelling [6]. The DAS28 is a measurement of ‘disease activity’, whereas the ACR20 measures change over time in such activity. Both include some indices which are subjective, e.g. number of tender joints (DAS28, ACR20), patient assessment of pain, and physician and patient global assessments of disease activity (ACR20) [5, 6]. The DAS and DAS28 include a subjective general health assessment (GHA) which can reflect factors other than joint inflammation, while the ACR20 includes a measurement of function, such as the health assessment questionnaire (HAQ) [4–6]. Thus, neither the DAS28 nor the ACR20 measures exclusively joint inflammation. The DAS28 and the ACR20 have been repeatedly used in various trials, particularly in assessments of the efficacy of DMARDs and biological agents. Rheumatologists have become so familiar with them that they may forget what it is that they actually measure.

In this issue of *Rheumatology*, Leeb and colleagues present the results they obtained using the DAS28 in a group of patients with RA compared with a group of patients with fibromyalgia (FM) [7]. Surprisingly, the two groups showed little difference in their DAS28 values. At first glance, the comparison appears to be bizarre. The DAS28, or other versions of the DAS, were not meant for assessing FM. Nevertheless, this apparently odd comparison makes one aware of both the strengths and the limitations of the DAS or any similar summation instrument. The DAS28 is based on two objective measures and two subjective ones: the former are the ESR and the number of swollen joints; the latter are the number of tender joints and the GHA. Leeb et al. found in their patients with RA that there was a high correlation between all the DAS components, both objective and subjective. This was not true in FM patients, where the GHA and the number of tender joints correlated well with each other but not with the number of swollen joints and the ESR, as one would expect in a non-inflammatory disease.

The presence of a large number of tender joints in FM is not surprising, and had already been reported by Reilly and Littlejohn [8]. This is consistent with the mounting evidence that FM is characterized by abnormalities in central pain processing [9]. Central pain processing may also be disturbed in RA [10]. Furthermore, patients with FM and RA both have a worse quality of life than healthy controls [11], thus influencing the GHA score. Factors other than inflammation may influence the number of tender joints in RA. For instance, FM occurs frequently in combination with RA [12]. Wolfe and Michaud found, in a study of more than 11 000 patients with RA, that 17.5% satisfied their survey criteria for FM [13]; these patients with both FM and RA had more pain, worse anxiety, more fatigue and greater work disability than patients with RA and no FM. Comorbidity with serious, potentially life-threatening diseases, such as diabetes, hypertension, ischaemic heart disease and cancer, was also significantly higher in patients with FM and RA [13]. Mortality was not reported but one must keep in mind recent studies that suggest that chronic widespread body pain, whatever its cause, appears to have a statistically significant association with decreased survival [14, 15].

Instruments used to measure the disease activity of rheumatic conditions other than RA are also affected by high pain levels and fatigue. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores in one study were higher in patients with FM than in patients with spondylarthritits [16]. In systemic lupus erythematosus the rating of disease activity was substantially affected by the presence of coexisting FM [17].

Changes in measures of disease activity have to be considered in relation to the background against which they occur. For instance, in a 12-week trial comparing etoricoxib, a COX-2 inhibitor, with naproxen and placebo in RA, 57.9% of those taking etoricoxib achieved ACR20 criteria [18]. This improvement was largely due to changes in several subjective measures, such as the number of tender joints, assessments of pain and disease activity (by patients and investigators) and the HAQ. The number of swollen joints decreased but the CRP showed no change. Similarly, celecoxib trials show that 51% of RA patients could achieve ACR20 criteria [19]. This is equivalent to the outcomes achieved in RA patients in the first 3 months of treatment with biological agents [20, 21].

Measures such as the number of tender joints, the pain severity, the GHA and the HAQ depend not only on current disease activity, but also on the extent and degree of the articular damage that has already occurred. Physicians and patients often disagree...
somewhat in their estimation of disease activity; comorbidity, function and educational level seem to exert a strong influence on patient perception, while physicians attach more importance to the number of swollen joints and laboratory values [22].

Pain ratings and self-reports are affected by several other factors, including mood, fatigue and self-censoring (avoidance of extreme ends of a pain visual analogue scale) [23]. We have little or no knowledge of the intra-rater reliability of pain and GHA. We do not know whether improvement or worsening of their disease leads to changes in patients’ pain threshold and tolerance, or changes in their expectations with a resetting of the way in which they grade GHA, or global disease assessment.

Pincus et al. reviewed the results of a trial comparing leflunomide, methotrexate and placebo; they compared the relative value of data obtained only from patient questionnaires with those obtained from the assessors, the additional contribution of laboratory results, and the full data sets [24]. The patient questionnaire data (pain, global assessment, and function), showed good agreement with the ACR20 and DAS in comparing the improvement seen in the patients treated with DMARDs; the assessor data, with or without the ESR, were not significantly better. Therefore, several cautions that one must raise, however; the assessor data included a count of tender joints, the results obtained compared two DMARDs of high efficacy with placebo, and the information obtained comes from one trial only. Nevertheless, this paper does show that patient responses can be used in determining treatment efficacy in RA.

We wish to make it clear that we think that both the DAS and the ACR20 are valuable indices, which continue to perform well in clinical trials. The ACR20 is used to measure change, while the DAS28 can be used to assess not only current disease activity but also change, by comparing scores over two or more points in time. The DAS28 lends itself to use in large studies as well as to clinical practice [25]; the rheumatologist’s awareness of the DAS28 and attempts to achieve specified lower scores improve patient care outcomes [26]. The mixture of subjective and objective measures is likely to be of greater theoretical concern than an actual problem. Leeb et al. found a high correlation between the subjective and the objective components of the DAS in their patients with RA [7]. Furthermore, we believe that parameters such as pain, tenderness and the GHA constitute essential information, although they may be affected by factors other than the inflammatory activity of RA. The question we have to ask is whether there would be an advantage in treating this information separately, since by so doing we would risk reverting to the proliferation of measures, which the DAS28 and ACR20 were designed to avoid. However, function, which is included in the ACR20 as an optional measure, deserves independent consideration. Anatomical changes will still require separate reporting.

Rheumatology does not have at its disposal measuring tools with the precision and accuracy of those available in specialties such as cardiology. There is no gold standard to assess clinical activity [27]. The DAS and ACR20 represent important advances in clinimetrics, but it is useful to be reminded, now and then, that they are imperfect and occasionally misleading.

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