EDITORIALS

PROVISIONAL GUIDELINES FOR MEASURING DISEASE ACTIVITY IN CLINICAL TRIALS ON RHEUMATOID ARTHRITIS

For many years disease activity in rheumatoid arthritis (RA) has been measured by an enormous number of different variables as a single golden standard for measuring disease activity is lacking. The validity of many of these variables is often questionable and not always evaluated. The EULAR Standing Committee on International Clinical Studies including Therapeutic Trials has recently proposed a minimal set of criteria to evaluate disease activity which should be used in all clinical trials of patients with RA. Advantages of including this set of criteria in all international clinical trials will be: (1) an improvement in the quality of clinical trials; (2) the option of comparing results of different drug trials; (3) the option of performing meta-analysis of those trials; (4) the possibility of developing uniform criteria of response.

Disease activity variables can be divided in Process and Outcome variables [1]. Process variables measure instantaneous disease activity whereas outcome variables measure the results of disease activity over a certain period of time [2]. Many variables measure a mixture of process and outcome: grip-strength and functional capacity for instance will be influenced by momentary disease activity as well as by irreversible joint destruction as a result of past disease activity. The acute phase proteins are solely process variables and a radiographic damage score is a pure outcome measurement.

In a prospective study of early RA patients in two departments of rheumatology at the University of Nijmegen and Groningen the validity of 10 frequently used single variables was tested [3]. The following proposal for a minimal set of variables to evaluate disease activity in RA was based on the results of this study completed with data from the literature [4-7].

**Process variables:**
- Number of tender joints
- Number of swollen joints
- Pain score on a visual analogue scale
- Patient global score on a visual analogue scale
- C-reactive protein or erythrocyte sedimentation rate (ESR)

**Outcome variables:**
- Health Assessment Questionnaire [8-10]
- Larsen Radiographic Score [11, 12]

It should now be further investigated whether it is possible to assess in a valid and simple way the other dimensions of outcome, for instance financial outcome, and psychological processes such as coping and adaptation.

Several studies have shown that a reduction in interobserver variability of the examination of joints for tenderness and swelling can be obtained by standardization [13]. This will directly influence the sample size required for clinical trials. When multiple observers are involved in a study this should be taken into account.

To facilitate the use of the clinical variables and thus to increase the validity one should use the simplest and easiest way to measure the joint scores. In an earlier cross-sectional study a 28-joint count appeared to yield as much information about disease activity as the traditional, more comprehensive, joint counts [14]. Using data from two controlled clinical trials a 36-joint score was found to be desirable based on many reliability and validity criteria [15]. In a prospective study of patients with early RA the validity of many different joint counts for tenderness and swelling were compared [16]. In addition, the option of grading or weighting of joint counts was studied [17]. The following validation criteria were included: reliability; construct validity (correlation with radiographic damage); correlational validity (with ESR and a patient global score on a visual analogue scale) and criterion validity (correlations with the health assessment questionnaire and the ability to discriminate between high and low disease activity). In this longitudinal evaluation it turned out that the 28-joint count (10 proximal interphalangeal joints; 10 metacarpophalangeal joints, two wrists, two elbows, two knees and two shoulders) for tenderness and swelling was at least as suitable as a measure of disease activity as the complete joint counts.

A further improvement in economical use of clinical variables might be obtained by the self-report articular index measurements [18, 19]. Longitudinal analysis of these variables are required before implementation in clinical studies is possible.

As disease activity cannot be expressed with one process or outcome variable one should probably evaluate response with a combination of these variables. It is possible to define response to treatment for an individual patient as well as for a group of patients with an index of disease activity. In a prospective study of patients with early RA an improvement of more than 1.08 in the Disease Activity Score (DAS) in an individ
differences in onset of action, this may give more reliable results than comparing the two treatments at a few fixed time points.

The EULAR Standing Committee for International Clinical Studies recently decided to validate and test that these disease activity variables be included in current trials whenever possible, in order to gain maximum experience in a short period of time.

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References