

Online publication

ARD launches an advanced online publication programme

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Selected papers will be published within days of acceptance

ARD *Online First* is an exciting innovation that will allow publication of selected articles within days of acceptance, and therefore months before they appear in the print version of the *Annals of the Rheumatic Diseases*. From February 2004 selected articles will appear in the raw manuscript form (not edited or typeset) in a new section on the ARD website (<http://www.annrheumdis.com>) indicated by the *Online First* logo (fig 1).

WHY DO WE NEED ONLINE FIRST?

Most medical journals have considerable delays between manuscript acceptance and publication in print, sometimes longer than a year. For practical reasons, at least some of this delay is unavoidable. However, we all agree that important clinical and scientific data should be available as soon as possible, especially where the information may impact clinical care. Advanced online publication goes some way towards meeting this need.

Rheumatoid arthritis

Patients with rheumatoid arthritis in clinical care

J S Smolen, D Aletaha

The challenge of following process, damage, and function

Rheumatoid arthritis (RA) differs from most other chronic inflammatory arthropathies in its high propensity towards joint destruction.¹ The mechanisms leading to this destruction are not fully elucidated, but pro-inflammatory cytokines and activation of osteoclasts appear to have pivotal pathogenic roles.²⁻⁴

The highly destructive nature of the disease is manifested by the development of erosions in 10–26% of patients



Figure 1 ARD *Online First* logo.

HOW WILL ONLINE FIRST WORK?

During the initial phase, we (the editorial team) will select two or three articles a week for advanced publication. The selection process aims at choosing papers with particular impact for clinicians, patients, and researchers. Authors will be asked for their permission to be part of *ARD Online First* and they will have an opportunity to proof the manuscript as usual before publication in the journal. The unedited manuscripts will be published weekly; edited, typeset versions may be posted as they become available. The final print version will be stamped with the *ARD Online First* logo (fig 1) and it will be high-

lighted on the table of contents within the issue. The ultimate print version will include the date of the initial online publication and all versions will be linked online. All articles are assigned a unique code—digital object identifier (DOI)—and guidance on how to cite the article will appear on the website.

Online First articles will be indexed by PubMed/Medline within days of publication, establishing primacy for the work. They will be searchable through the usual search engines (PubMed, Google, etc) and through ARD Online; search results will default to the most recent version.

Annals of the Rheumatic Diseases is the first of the specialist journals published by the BMJ Publishing Group (<http://www.bmjournals.com>) to launch an *Online First* programme (the weekly *BMJ* started its advanced online publication section in December 2003).¹ *ARD Online First* is an experiment and we welcome comments from authors and readers—both positive and critical—so that we can optimise the service and accompanying procedures. If the pilot is deemed a success the programme may be expanded so that most accepted articles are available *Online First*.

We are confident that this exciting new feature will be valued by all who may profit from *ARD*, including clinicians, researchers, and, last but not least, patients.

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was 36% within 2 years.⁹ The degree of joint destruction accrues with time,^{10 11} and increasing radiographic joint destruction correlates with decreasing function as measured by patient questionnaires.¹²

FUNCTIONAL ASSESSMENT BY SELF REPORT QUESTIONNAIRES

Functional assessment by self report questionnaires has become standard in randomised clinical trials¹³⁻¹⁷ as well as clinical research. The most commonly used among the many questionnaires¹⁸ is the Stanford Health Assessment Questionnaire (HAQ)¹⁹ and its derivatives. These questionnaires measure primarily function and health related quality of life, the improvement of which is the most important aspect in the care for our patients. Nevertheless, these questionnaires do not allow differentiation between the degree to which an impairment in functional activity is due to current disease activity (and thus is process related and poten-

tially reversible), and the extent to which it is a consequence of accrued, long term, largely irreversible damage (and thus constitutes a reflection of the process induced outcome).

The original HAQ comprises 20 questions in eight categories, and a score of 0 (no difficulty), 1 (some difficulty), 2 (much difficulty or need for assistance), or 3 (unable to perform) is given to each question; the highest score in each category represents the score for that category¹⁹ and the sum is then divided by the number of categories, yielding the total HAQ score (0–3). It should be borne in mind that the overall score does not consider which area of “health” or “daily life” constitutes a priority of improvement for the individual patient. These health preferences and the perception of changes may differ between patients and physicians.^{20–22} Consequently, an improvement in HAQ score does not necessarily imply that the areas which are most important to the patient have improved. Thus, although patient centred, current functional assessments may not fully appreciate the patient perspective. Despite these limitations, the HAQ constitutes a well validated tool that reflects process and outcome.²³ Although other functional measures may allow more functional insights, the ease of the application of the HAQ makes it an attractive tool for clinical practice.¹⁸

“An improved HAQ score may not mean that the areas important to the patient have improved”

The HAQ scores increase with increasing disease duration and are importantly determined by joint damage in longstanding disease.^{12 23–25} Nevertheless, even in longstanding disease, disease activity appeared to be a major factor influencing functional capacity.^{23 24}

In a recent study it was noted that after 12 months HAQ scores declined by about 75% among patients with very early (<3 months' symptom duration) RA treated with disease modifying anti-rheumatic drugs (DMARDs) compared with <40% improvement in patients in whom institution of similar DMARD regimens was delayed by a few months, both groups starting at HAQ scores of about 0.9.²⁶ In parallel, disease activity, as assessed by the disease activity score (DAS28),²⁷ decreased by about 50% and 30%, respectively, reaching the area of low disease activity in patients with very early arthritis. In contrast with such investigations on very early arthritis, in pivotal trials of combinations of methotrexate with etanercept (24 week trial)

or infliximab (54 week trial) in patients with long established RA, baseline HAQ scores were 1.5 or 1.8, respectively, and improvement amounted to about 45% and 30%, while the placebo responses were about 25% and 10%; mean disease duration was about 13 and 11 years, respectively.^{28 29} In a 24 week trial of leflunomide, in which starting HAQ scores were 1.1 at baseline, improvement by about 45% was seen with leflunomide compared with 30% with sulfasalazine and <10% with placebo; mean disease duration in that population was about 7 years.³⁰ Changes with anakinra treatment fall into about the same range.³¹

Trials cannot be compared easily owing to differences in the patient groups investigated. Nevertheless, several lines of information can be drawn from these trials^{26 28–32} as well as from observational studies^{24 25}:

- DMARD treatment improves HAQ scores significantly. Over the course of 6 months to 2 years, the usual duration of these trials and their extensions, HAQ scores do not deteriorate in patients with highly active disease, even if treated with placebo; rather, they often improve slightly with placebo, and, therefore, an improvement of more than –0.22 has been determined as minimum important difference.^{33–35} With treatment with DMARDs or biological agents, HAQ improves by more than –0.5 in many patients, in some trials even in >50% of the patients.³² This degree exceeds more conservative results on the significant change of the HAQ from the patients' perspective in clinical settings, which amounts to at least –0.31 at an 80% confidence level, and at least –0.48 for 95% confidence.³⁶ Thus, effective DMARD treatment affects the HAQ score significantly, whether in clinical trials or practice, but even with placebo there is some improvement in HAQ in clinical trials, although this rarely exceeds the minimum important difference on a group level. (In this respect it is important to mention that laboratory surrogates of disease activity, such as C reactive protein (CRP), usually decrease significantly with effective DMARD treatment but show little or no change with placebo.)
- Structural damage does not impact HAQ scores in the shorter term. Because radiographic changes deteriorate significantly in placebo treated patients, these destructive events are not reflected in a deterioration of HAQ scores and thus do not lead to

an impairment of functional activities in the relatively short term. This conclusion is in line with the findings, that joint destruction impacts HAQ scores mainly in the long term—that is, as a consequence of its accumulation over time.^{12 24 25} It also indicates that despite their significant rise, increases of radiographic scores over the time followed in clinical trials are too small to affect function. Moreover, HAQ scores are related more to destruction of large joints than to those of small joints,²⁴ and the large joints are usually not evaluated for radiographic changes in clinical trials.

- Structural damage does impact HAQ scores in the longer term. Comparing HAQ scores and disease duration in different trials at baseline, one might extrapolate that among patients fulfilling the entry criteria for clinical trials, disability scores increase with increasing disease duration (and increasing numbers of DMARD failures). Moreover, despite the significant effects of all these treatments on disease activity, the association of HAQ scores with disease duration was maintained even at the end of the trials: approximate HAQ scores at study end were 0.9 in the etanercept/MTX trial, 1.3 in the infliximab/MTX trial, and 0.6 in the leflunomide trial, whereas—after one year of traditional DMARD treatment—amounted to 0.5 in patients in whom DMARDs were started at a median of about 12 months' disease duration and to 0.2 in those in whom treatment was started within about 3 months (and <5 months²⁶) from onset of symptoms. Thus, with increasing disease duration the fraction of the HAQ score determined by disease activity shrinks compared with that determined by irreversible changes in patients with long term RA. These findings extrapolated from recent clinical trials are in line with the prospective data on the association of HAQ with long term radiographic damage.^{12 24 25}
- HAQ scores reflect disease activity to an important extent. It appears—on the basis of the above trial patient groups—that about 0.3–0.7 HAQ score units are governed by disease activity. It should be noted that such extrapolation from trial data refers to mean values, that remissions are only rarely seen in clinical trials, and that, consequently, further reduction of disease activity may lead to even more reduction in HAQ scores. Moreover, changes in HAQ score may vary in different individual patients. However, these data indicate that,

regardless of duration of disease, the HAQ score does partly reflect disease activity and this to an important extent.^{24 25 37}

- The proportionate contribution of disease activity and damage to total HAQ scores is unknown. Given that the HAQ is an important outcome in most clinical trials on new therapeutic drugs, it should be borne in mind that these trials provide a rather short term view of treatment effects. Although retardation or even arrest of progression of destruction can be shown in many patients in such trials, such retardation would have to be over a long period of time, rather than the usual one year time-frame of radiographic studies in clinical trials, to materialise into clinical benefit, and thus the essential variable (and target) of most short term treatments is disease activity. Therefore, the proportion of the HAQ score that is primarily explained by disease activity, determines the therapeutic potential. It would be most desirable to estimate the impact of disease activity on function or quality of life, maybe by deduction of an activity adjusted HAQ score; vice versa, such a score could allow deduction of a measure for the impact of accrued damage on function or quality of life. In a group comparison, changes in such a score would better reflect the effects of an intervention on damage related impairment.

“The proportion of the HAQ score that is explained by disease activity determines the therapeutic potential”

EARLY REFERRAL: DAMAGE LIMITATION

That clinical disease activity is associated with the acute phase response has been convincingly shown repeatedly.³⁸⁻⁴⁰ That damage increases as a consequence of a longstanding active rheumatoid process, has also been determined convincingly by the association of the cumulative acute phase response with radiographic progression of joint destruction³⁹⁻⁴¹ as well as by the association of joint inflammation with the occurrence of erosions.^{24 40-42} Thus, combating the active inflammatory process is the most important protective measure, and the earlier, the better.^{5 26 43-47} However, to this end, it is not only necessary to diagnose RA early and to start DMARD treatment early in the disease course but also equally important to refer patients with inflammatory arthritis early to the rheumatologists, because delay of referral is still

one of the major problems related to delay in treatment initiation.^{48 49} Early arthritis clinics are in existence in many centres⁵⁰⁻⁵² and have disclosed the value of early treatment, which has already briefly been eluded to above. But strategies to refer patients to these clinics have not been well elaborated. We ourselves have chosen to inform general practitioners about RA, the importance of recognising it early, and the foundation of early arthritis clinics, through the monthly journal of the Austrian Chamber of Physicians⁵³ as well as the mass media. More recently, an evidence based clinic guide for early referral has been established,⁵⁴ which may serve as a basis for such early referral, but ought to be made known widely to general practitioners as well as patients. Diagnostic, or better: prognostic algorithms, have also been proposed by several groups,^{42 51 55-60} but their validity across patient populations is not yet established. Such algorithms are currently discussed, in an international working group dealing with *diagnostic criteria in early rheumatoid arthritis* (DICERA).⁶¹ The group held its third meeting in August 2002 in Bethesda, MD, discussing new diagnostic and, particularly, therapeutic strategies as well as collaborative studies on very early inflammatory polyarthritis.

“To achieve remission, patients with RA must be monitored every 2-3 months”

Because consequent control of disease activity is pivotal to preventing or at least retarding long term damage and because traditional DMARDs may have significant, but still limited, effectiveness in this respect,⁶²⁻⁶⁵ it is important to define stringent therapeutic aims as well as to follow up patients subsequently in daily practice. Mild disease is still active disease and may be slowly leading to significant joint destruction and disability.

The most important aim in RA treatment is remission,^{66 67} and although this is rarely reached in clinical trials, it is achievable in up to 25% of clinic patients.^{56 68} With strategies aiming at increasing the dose of monotherapy, combining treatments in a step-up approach and, especially, switching strategies within the short term if a DMARD course fails, partial remissions with no more than two or three affected joints are seen in our clinics in an even much larger additional proportion of patients. However, to achieve such or even better goals, patients need to be monitored every 2 to 3 months, as long as they do not reach a state of “no evidence of active disease”, in order that the switch of therapeutic strategies can be timely.

EVALUATION OF DISEASE ACTIVITY

ACR criteria, DAS, and EULAR response criteria

For the evaluation of disease activity, a combination of surrogates related directly to the inflammatory events, such as joint counts and the acute phase response, have been successfully employed over the past decade.^{13 27 69-71} Although the American College of Rheumatology (ACR) response criteria have been developed to compare improvement from baseline in cohorts of patients, they do not allow assessment of “actual” disease activity, and thus neither comparison of clinical status between groups of patients nor between individual patients is possible. In contrast, the employment of a numerical measure from baseline throughout the disease course, as provided by the DAS and the EULAR response criteria, allows a comparison of the disease status of patient cohorts as well as individual patients.^{71 72} This is an important advantage, if disease activity measures are to be successfully employed in clinical practice. Nevertheless, calculation of the DAS, and also of the ACR response, is relatively complicated and requires the use of a calculator. Therefore, simpler activity indices could be of particular help to allow transference of activity scoring into daily clinical practice.

Simplified disease activity index (SDAI)

Aiming at obtaining a simple disease activity measure, we have recently developed the simplified disease activity index (SDAI), which is the linear sum of five core set variables: tender joint and swollen joint count based on a 28 joint assessment, patient and physician global assessment of disease activity, and CRP.⁷³ Changes of the SDAI have been found to correlate very well with changes of the DAS, of the ACR response, and also with HAQ scores and radiographic changes. Furthermore, a truncated SDAI, summing the values of all variables with the exception of CRP,⁷³ was equally reliable, allowing a validated disease activity measure to be obtained during the office visit of the patient, without having to wait for a laboratory result. Thus, tools are available to document patients' disease activity simply and reliably, whether by using only a patient questionnaire⁷⁴ or a combination of questions to the patient and physician's assessment, such as the SDAI.⁷³ Also, the calculation of the DAS has become simpler because an automated calculator has become available. However, it should be borne in mind that validation

of response criteria has been mostly obtained using data of clinical trials. Thus, more validation is required before response criteria are fully adopted for clinical practice. In such research their value for daily practice settings will be best assessable. To this end, the measurement error of assessing joint counts or using health status measures repeatedly needs to be taken into account,^{23 34–36 75} and in clinical practice a definite improvement or deterioration could be defined as a change that exceeds such measurement error.

ADVERSE EVENTS

The follow up of patients also requires looking for adverse events. Interestingly, laboratory abnormalities tend to occur mainly during the first 3 to 4 months of DMARD treatment and are much rarer during subsequent months⁷⁶; thus, once patients have tolerated DMARDs for 4 months or more, tight laboratory monitoring does not appear to be necessary.

“Most adverse events occur during the first few months of DMARD treatment”

SUMMARY

Taken together, our current clinical armamentarium to follow the course of RA offers several disease activity measures. Evaluation of radiographic destruction, but also of anatomical changes such as malalignment,⁷⁷ can serve as outcome measure, because these changes best reflect the damage related to the pathological process in and around the joints; whether radiological changes can be reversible, is still a matter of debate.⁷⁸ Assessment of function reflects the combination of disease activity and damage. Questionnaires or other instruments which only determine functional improvement due to irreversible damage are not (yet) available. However, their development could lead to interesting, new clinical insights. Likewise, basic science has not yet provided us with tests that reflect the destructive process reliably. Measuring disease activity by surrogate measures such as the acute phase proteins does not reflect destruction at a single point in time.

In conclusion, assessment of disease activity, damage, and functional capacity are equally important also in clinical practice; RA, if insufficiently controlled, may be a highly destructive disease. Achieving low disease activity, ideally a remission-like state, is pivotal to improving prognosis.⁷⁹ Current treatments and early institution of DMARDs allow this aim to be accom-

plished in many patients. However, decisions to switch (or to maintain) treatment require recording of the patients' clinical status, and in many healthcare systems the use of costly treatments, as increasingly employed, requires justification which, again, can only come from recorded data.¹⁸ Rather than guessing disease activity and quality of life, providing evidence will validate decisions and improve quality of care. A combination of a more physician centred activity score, such as the SDAI or similar, with a patient centred functional measure, such as the HAQ or similar, in conjunction with an occasional evaluation of the radiographic situation, will give all necessary information for the longitudinal observation of patients' disease state in clinical practice. The tools are available and so relatively easy to use.

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