Development of a disease activity index for the assessment of reactive arthritis (DAREA)

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Abstract

Objectives. The objectives of this study were to investigate and validate individual variables and to develop a composite score for disease activity measurement in patients with reactive arthritis (REA).

Methods. In the first cross-sectional part, the clinical and laboratory evaluation of 45 patients was used to elaborate the most important individual disease activity measures. In the second prospective part, these variables as well as a composite score for disease activity measurement of REA were prospectively validated in 23 patients at two points in time.

Results. The following variables emerged as the most useful for the composite measure: number of swollen and tender joints, patient’s pain and global assessment, and C-reactive protein. The score was calculated by simple addition of the individual figures.

Conclusion. DAREA constitutes a reliable score which can easily be assessed on a day-to-day office work basis.

Key words: Disease activity, Reactive arthritis, Outcome measurement.

Reactive arthritis (REA) is a sterile mono- or oligo-arthritis which evolves several days or weeks after an infection, usually of bacterial origin, most commonly involving the urogenital or gastrointestinal tract [1]. REA can be triggered, for example, by Salmonella, Yersinia, Chlamydia and Mycoplasma species [1–3]. The disease is commonly associated with HLA-B27 and has a temporal relationship to the infection [1, 4].

Characteristically, and in contrast to classical infectious arthritis, the agent(s) cannot be cultured and therefore, may not be ‘viable’ once having reached the joints. However, using sensitive detection methods, such as immunohistology, electron microscopy and polymerase chain reaction, evidence of the presence of infectious agents within the joint fluid or synovial membrane has been found [5–7].

Thus, it is assumed that cells (probably/likely of the monocyte lineage) containing infectious agents or their fragments gain access to the joint and induce a cellular immune response, which does not lead to rapid and complete elimination of the inciting agent, but rather to a ‘smouldering’ immune response with persistence of the causative organism and thus to subacute or chronic arthritis.

On the basis of these events it has been postulated that therapy with antibiotics could reduce the duration of the disease and prevent chronic arthritis [8–11]. Although the symptoms also commonly resolve spontaneously after weeks to months, chronic courses can occur and often necessitate more ‘aggressive’ therapy with disease-modifying anti-rheumatic drugs (DMARDs) such as sulphasalazine, gold compounds or methotrexate [12, 13]. There exist only a few systematic studies on the issue of the effectiveness of these or other therapeutic approaches. This is in part due to the lack of established disease activity criteria which can be followed prospectively and reliably in controlled studies.

Disease activity criteria have been established for several chronic inflammatory rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [14–17]. In RA, a large number of clinical and laboratory variables have been analysed, and based on preliminary research on activity and outcome indices or scores, core sets have recently been agreed upon by several international organizations [16–18]. These sets of variables intend to use a limited number of parameters best suited for monitoring disease activity and/or therapeutic efficacy in a longitudinal way. Such scores can also be used to establish a numerical value for disease activity, such as the disease activity...
score, which may allow improved analysis of therapeutic response or progression of disease [14, 19].

More recently, a disease activity score has been proposed for ankylosing spondylitis [20], another HLA-B27-associated disease which, in contrast to REA, involves predominantly the spine rather than the peripheral joints.

In order to allow for an improvement in the follow-up of REA patients, particularly those in whom the disease runs a chronic course, we searched for a possible set of variables as a first step in the development of a disease activity score for REA. To this end, we evaluated the validity of commonly used variables for the assessment of disease activity in REA by analysing these variables individually in a cross-sectional study. Then, in a second prospective investigation of REA in patients who underwent antibiotic therapy, all these variables were evaluated again individually. In addition, a composite index derived from those variables which had been found most useful as a result of the first cross-sectional study was tested. The data obtained show the derivation and reliability of a disease activity index for REA (DAREA) which is also very easy to calculate on a day-to-day basis.

**Patients and methods**

*Study design and investigations*

The study was composed of two parts: first, in a cross-sectional investigation the clinical and laboratory data from 45 consecutive REA patients were evaluated in order to derive the variables most useful for following disease activity in REA and possibly to obtain a minimal set of variables suitable for the calculation of a disease activity score. In the second part of the investigation, a group of 23 additional patients were investigated prospectively at two points in time, one at first presentation to the clinic and the other at the last follow-up visit during or immediately after therapy.

REA was defined as a sterile oligoarticular joint inflammation that developed after a distant infection originating in the urogenital or gastrointestinal tract.

The diagnostic management of the patients in both parts of the study was identical and based on international diagnostic criteria developed by consensus [21]. In particular, the presence of at least one swollen joint for at least 2 weeks was mandatory. In addition, RA, ankylosing spondylitis, psoriasis, crystal arthropathies, septic arthritis, and a history of inflammatory bowel disease had to be absent. Extra-articular manifestations, a history of urethritis, enteritis or cervicitis were not mandatory.

A detailed history, including that of previous infections or sexually transmitted diseases, of symptoms of urethritis, conjunctivitis or enteritis, but also of joint problems and low back pain, was taken. A complete physical examination and laboratory investigations were performed in every patient. This included evaluation of the total joint count for swelling and tenderness. For the prospectively studied group, all data (clinical and laboratory evaluations) were repeated at the last control examination. Clinical evaluations, including joint examinations, were performed by the same assessor in each individual patient. The assessor in the first part of the study was different from the assessors in the second part. The assessors were physicians with at least 3 yr of rheumatological experience.

The following laboratory tests were performed: complete blood cell count, routine blood chemistry, erythrocyte sedimentation rate (ESR; mm/h), C-reactive protein (CRP; mg/dl), rheumatoid factor (RF) and HLA-B27. Antibody titres for *Salmonella* species and *Yersinia enterocolitica* (immunoperoxidase assay and Gruberin a second prospective investigation of REA in patients Widal agglutination tests kindly performed by the Institute of Hygiene of the University of Vienna) were measured. Genitourethral swab cultures (for *Chlamydia* and *Mycoplasma*), antibody titres for *Chlamydia* (tested by IPA Zyme Chlamydia, Savyon) and stool cultures (for *Yersinia enterocolitica, Salmonella, Shigella* and *Campylobacter*) were performed in each patient [22].

Standard radiographs of involved joints as well as lumbar spine and sacroiliac joint X-rays, when low back pain was reported, were taken.

*Study populations*

The cross-sectional study group consisted of 45 patients (14 females and 31 males) with an age range of 19–73 yr (median: 37). Mean disease duration was 5.3 ± 3.3 weeks. In this group a mean of 2.0 ± 1.1 (median 2) swollen peripheral joints and a mean of 2.7 ± 1.9 (median 2) tender peripheral joints were involved. Recent onset low back pain was present in 17 (38%) of the patients, none had early morning pain and four had pain upon examination of their sacroiliac joints. Radiographic investigations did not reveal erosions in any of the patients’ peripheral joints. In four patients evidence of saccroilitis was found by conventional radiography. The following joints were involved: knee joints in 22, ankle joints in 15, metatarsophalangeal joints in 11, toe interphalangeal joints in 11, metacarpophalangeal joints in six, wrists in four, and hip joints in three patients. Synovial fluid was obtained in 12 patients; the mean cell count was 7460 ± 3730 cells/µl.

All patients were negative for RF by nephelometry. HLA-B27 was positive in 60% of the patients. Genitourethral infections were diagnosed by positive swab cultures in 28 patients (*Mycoplasma hominis* in 22, *Chlamydia trachomatis* in five, both in one), an additional 11 patients had a titre of anti-chlamydial antibodies ≥1:16 IgA and ≥1:512 IgG (values in healthy individuals: IgA < 1:16 and IgG ≤ 1:64; cut-off values: IgA: 1:16, IgG: 1:256). Genitourethral symptoms (burning sensations) were reported by four patients. Six patients had enterobacterial infections (three with *Salmonella* species and three with *Yersinia enterocolitica*, as determined by high antibody titres to these bacteria). A history of intestinal symptoms was present in all of
these six patients. Stool cultures, however, were negative in all patients. Eye involvement (conjunctivitis) was seen in one patient.

The prospective study group consisted of 23 patients (nine females and 14 males) with an age range of 21–65 yr (median 30). Mean disease duration was 6.1 ± 3.4 weeks. A mean of 2.5 ± 1.3 (median 2) swollen peripheral joints and 3.3 ± 1.7 (median 3) tender peripheral joints were involved. Recent onset low back pain was present in four patients (17%). None had night pain and none had pain upon examination of their sacroiliac joints. No erosions were seen on radiographic joint examinations, and evidence for sacroilitis was not found in any of the patients. RF was negative in all patients, HLA-B27 was positive in 30% of the tested patients. The following joints were involved: knee joints in 12, ankle joints in 12, wrist joint in four, MTP in two, MCPs in two, and hip and shoulder joints each in one of the patients. Synovial fluid was obtained in five patients; the mean cell count was 7570 ± 2370 cells/μl.

Genitourthral infections were detected by culture in 16 patients (five with Mycoplasma hominis, nine with Chlamydia trachomatis, and two with both), genitourthral symptoms (burning sensations) were reported by one patient. Seven patients had evidence of enterobacterial infections (five with Salmonella species, two with Yersinia enterocolitica, diagnosed by high antibody titres to these bacteria). Five of these patients reported intestinal symptoms (diarrhoea). The patients were investigated at first presentation and at 6 weeks after the institution of antibiotic therapy. All patients received non-steroidal anti-inflammatory drugs (NSAIDs; mainly diclofenac or ibuprofen). Antibiotic treatment consisted of tetracyclines (n = 6), macrolides (n = 11) or quinolones (n = 6) in conventional doses.

Variables selected for analysis

The following variables were recorded for evaluation: number of swollen joints (usually 0–5), number of tender joints (usually 0–5), low back pain (absent = 0, moderate = 1, severe = 2), patient’s pain assessment (0 = none, 1 = moderate, 2 = severe), patient’s global assessment (0 = well, 1 = fair, 2 = poor), eye involvement (none = 0, moderate = 1, severe = 2), subjective symptoms of urethritis (no symptoms = 0, burning = 1, discharge = 2), intestinal symptoms (none = 0, diarrhoea = 1), ESR (mm/h), CRP (mg/dl), leucocyte count, haemoglobin, platelet count, physician’s global score (on a 5-point scale, ranging from 1 = symptom-free, to 5 = very severe), and a 10 cm visual analogue scale (VAS, 0.0 = very well, 10.0 = worst possible) for both pain and global assessment, by the patients.

Statistical evaluation

In both patient groups summary statistics are indicated as medians and ranges. In the cross-sectional study group the non-parametric Kendall correlation coefficient was used to analyse correlations between individual variables as well as between the physician’s global assessment and the disease activity score derived from the data. For comparison between the first and the last visit in the prospective study group, the Wilcoxon test was employed. P values < 0.05 were considered significant. Data were processed using the SAS-program (Statistical Analysis System, Version 6.11; SAS Institute Inc, Cary, NC, USA).

Results

Analysis of variables in the cross-sectional study group

The cross-sectional analysis revealed significant correlations between many clinical variables as well as between many clinical variables and CRP (r up to 0.79). For the purpose of clarity, in Table 1 only correlations between the physician’s global assessment and the different variables are shown. The physician’s global assessment could be exchanged for the patient’s global assessment or VAS results without substantially changing the results (data not shown). The physicians’ global assessment was chosen for comparison because in this study, like in early phases of the development of other scores for which there is yet no gold standard for such purpose available, variables commonly used for the evaluation of disease activity were assessed, and it is presently mostly the physician who assesses such variables and disease activity in general.

The following variables correlated significantly with the physician’s global assessment of disease (Table 1): number of swollen joints, number of tender joints, patient’s pain and patient’s global assessment (both by the 3-point scale and by the VAS), low back pain and the laboratory measures CRP, haemoglobin and leucocyte count. There was an inverse relationship with haemoglobin.

For reasons dealt with in detail in the discussion, the following variables were selected to compose DAREA: swollen joint count, tender joint count, patient’s pain and patient’s global assessment (by 3-point scale), and CRP (in mg/dl). The reason for selecting the 3-point scale rather than the WAS was the ease with which it can be added to the other numerical values allowing for easy and rapid calculation of the DAREA score, namely by simply adding up the numerical values obtained for each of these five items. On this basis, in the cross-sectional group a DAREA range of 4.0–22.5 (median 10) was found, and DAREA obviously correlated very well (P < 0.0001) with the physician’s global assessment (Fig. 1A).

Prospective validation of DAREA

In order to validate DAREA, a prospective study of 23 patients was performed. DAREA was recorded at first presentation and after 6 weeks, i.e. during or shortly after therapy. Table 2 shows the data for each variable at the first and the last visit. Almost every single variable improved between the first and the last visit, indicating amelioration of the disease with time or/and therapy. DAREA amounted to a mean of 12.9 ± 5.8 at the initial visit and decreased to 2.7 ± 0.7 at the final observation
Disease activity index for REA

Table 1. Clinical and laboratory variables in the cross-sectional patient group derivation of the DAREA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± s.d.</th>
<th>Median</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of swollen joints</td>
<td>2.0 ± 1.1</td>
<td>2.0</td>
<td>0.383</td>
<td>0.013</td>
</tr>
<tr>
<td>No. of tender joints</td>
<td>2.7 ± 1.9</td>
<td>2.0</td>
<td>0.410</td>
<td>0.006</td>
</tr>
<tr>
<td>Low back pain</td>
<td>0.4 ± 0.5</td>
<td>0.0</td>
<td>0.15</td>
<td>0.353</td>
</tr>
<tr>
<td>Urogenital symptoms</td>
<td>0.08 ± 0.3</td>
<td>0.0</td>
<td>0.27</td>
<td>0.09</td>
</tr>
<tr>
<td>Intestinal involvement</td>
<td>0.13 ± 0.3</td>
<td>0.0</td>
<td>-0.03</td>
<td>0.81</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>0.02 ± 0.14</td>
<td>0.0</td>
<td>0.15</td>
<td>0.353</td>
</tr>
<tr>
<td>Patient’s pain assessment</td>
<td>1.7 ± 0.4</td>
<td>2.0</td>
<td>0.708</td>
<td>0.0001</td>
</tr>
<tr>
<td>Patient’s global assessment</td>
<td>2.5 ± 2.5</td>
<td>2.0</td>
<td>0.568</td>
<td>0.0001</td>
</tr>
<tr>
<td>VAS pain assessment (patient)</td>
<td>6.6 ± 1.2</td>
<td>7.0</td>
<td>0.792</td>
<td>0.0001</td>
</tr>
<tr>
<td>VAS global assessment (patient)</td>
<td>6.1 ± 1.3</td>
<td>6.0</td>
<td>0.774</td>
<td>0.0001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>32.3 ± 21.9</td>
<td>28.0</td>
<td>0.189</td>
<td>0.146</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>2.7 ± 2.9</td>
<td>2.0</td>
<td>0.341</td>
<td>0.013</td>
</tr>
<tr>
<td>Leucocytes (× 10^9)</td>
<td>7.6 ± 2.0</td>
<td>7.5</td>
<td>0.407</td>
<td>0.008</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13.5 ± 1.2</td>
<td>13.4</td>
<td>-0.356</td>
<td>0.018</td>
</tr>
<tr>
<td>Platelets (× 10^9)</td>
<td>297.7 ± 88.5</td>
<td>287.0</td>
<td>0.282</td>
<td>0.061</td>
</tr>
<tr>
<td>Physician’s global score</td>
<td>4.4 ± 0.8</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Correlation to physician global score. Components of DAREA are in bold.

(P < 0.0001). As in the cross-sectional study, the change in the physician’s global assessment and the change in DAREA were related to each other, and thus DAREA was highly significantly associated with the physician’s global assessment both at the beginning and at the end of the observation period (Fig. 1B).

In several patients, DAREA was assessed not only at two visits, but also in between. As can be seen in Fig. 2, there was a consistent decrease of DAREA over time in most of the eight patients, although in two of them DAREA remained high, indicating failure to remit.

**Stratification according to joint counts**

When prospectively studied patients were stratified into two groups, one with one or two joints involved (n = 8), the other with three or more joints involved (n = 15), the following results were obtained: patients with one or two involved joints had an initial mean DAREA of 8.2 ± 4.8 (range 2–18) which fell to 2.9 ± 2.9 (range 0–8) at the last visit. Patients with three or more swollen joints started with a DAREA of 15.4 ± 4.6 (range 9–25) and had a DAREA of 2.5 ± 3.0 (range 0–8) at the last visit. Thus, in both subgroups DAREA fell significantly over time and discriminated well between active and inactive disease.

**Actual example for calculating DAREA**

A patient was found to have his left knee joint, his IP of the right third toe and his right MTP II swollen (score 3); these joints and right MTP IV were tender (score 4); the patient assessed his global status as being 2 and his pain status as 3 (very painful, because he can hardly walk despite NSAID therapy); his CRP amounted to 4.2 mg/dl. Thus, the total DAREA was: 3 + 4 + 2 + 3 + 4.2 = 16.2.

**Evaluation of validity**

**Face validity/content validity.** Each variable chosen, be it clinical or laboratory, can be affected by the disease: REA goes along with joint swelling and pain in joints and occasionally with involvement of the lower back; it is an inflammatory disorder with the respective laboratory abnormalities; and it leads to subjective complaints of pain and of sickness. Of the many variables investigated, the composition of the DAREA score takes two variables assessed by the physician, two variables reported by the patient, and one laboratory variable into account.

**Criterion validity.** A significant association was found between DAREA and the physician’s global assessment, which is currently the major means to assess disease activity. Moreover, remission is the most important response in REA. Patients in remission (as judged by the treating physician) had a normal DAREA, while the index was high in the initial phases when the disease was most active.

**Construct validity.** The improvement of DAREA, if obtained at several points in time in patients going into remission, was highly significant (Figs 1B, 2). In contrast, patients not going into remission continued to present with a high DAREA score (Fig. 2).

**Discussion**

In this study we have developed and validated DAREA, which is reliable and easy to calculate. In general, disease activity scores can be helpful both for clinical studies and day-to-day patient care. In clinical practice the judgement of disease activity varies considerably (score 3); these joints and right MTP II swollen (score 3); these joints and right MTP IV were tender (score 4); the patient assessed his global status as being 2 and his pain status as 3 (very painful, because he can hardly walk despite NSAID therapy); his CRP amounted to 4.2 mg/dl. Thus, the total DAREA was: 3 + 4 + 2 + 3 + 4.2 = 16.2.
most accurately, a cross-sectional study of variables employed to judge disease activity was performed and the results obtained used for further evaluation. The physician’s global score was chosen as the main parameter for the comparisons, since there is no other ‘gold standard’ available and since it is the physician who currently usually ‘judges’ disease activity. However, no different results would have been obtained if patient-derived variables had been used (data not shown).

The excellent correlation between the physician’s global assessment and the other variables as well as the DAREA score could lead to the conclusion that it would be sufficient to just have the physician (or the patient) judge disease activity. However, a disease activity score should also allow less-experienced physicians to assess disease activity in REA and reach similar conclusions as experienced ones. Furthermore, DAREA should help in the evaluation of patients who judge their disease differently due to psychological or cultural factors. Finally, inaccuracies in scores of individual variables are smoothed out by combining several variables which have different sources, such as the patient, the physician, and the laboratory, as long as they correlate with the response. The best response, i.e. remission, is indicated by a normal DAREA (< 1). Although DAREA, for obvious reasons, differed between patients with one or two and those with more inflamed joints, it discriminated well between active and inactive disease even in those with only a few involved joints.

The five components of DAREA are: number of swollen joints, number of tender joints, patient’s pain and global assessments, and CRP (mg/dl). The inclusion of joint abnormalities is obvious, since arthritis is what we deal with. However, the inclusion of both swollen and tender joints is based upon the observation that tenderness often lasts longer than swelling in many forms of arthritis, which is particularly true for REA. In fact, joint tenderness correlated to a higher degree with the physician’s global assessment and other variables than swelling. However, since synovitis is the major pathological process in REA, swelling was also included. Low back pain was not included, since it occurred in only about a third of the patients and had therefore individual points may reflect more than one patient. There was excellent correlation for both points in time as well as for the total analysis ($P < 0.0001$).

Therefore, the attempt of this study was not only to search for a disease activity score where there is hitherto none available, but also to allow easy handling of such a score for the practising clinician. Nevertheless, as with all other disease activity scores, this one should undergo further validation in other centres and/or in consensus finding study groups [17–19, 25].

To determine which factors would be best combined to produce a score which reflected the disease activity
Disease activity index for REA

Table 2. Clinical and laboratory variables at first and last visit in the prospective study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>First visit Mean ± s.d.</th>
<th>Last visit Mean ± s.d.</th>
<th>P &lt; (visit 1 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of swollen joints</td>
<td>2.5 ± 1.3</td>
<td>0.3 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of tender joints</td>
<td>3.3 ± 1.7</td>
<td>0.9 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low back pain</td>
<td>0.2 ± 0.4</td>
<td>0.0 ± 0.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Urogenital symptom</td>
<td>0.04 ± 0.2</td>
<td>0.0 ± 0.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Intestinal involvement</td>
<td>0.21 ± 0.4</td>
<td>0.0 ± 0.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Patient's pain assessment (3 points)</td>
<td>1.8 ± 0.5</td>
<td>0.3 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patient's global assessment (3 points)</td>
<td>1.8 ± 0.5</td>
<td>0.3 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VAS pain assessment (patient)</td>
<td>7.0 ± 1.9</td>
<td>2.4 ± 1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VAS global assessment (patient)</td>
<td>6.8 ± 1.9</td>
<td>2.4 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>44.8 ± 34.5</td>
<td>19.0 ± 14.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>3.5 ± 3.8</td>
<td>0.8 ± 1.2</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Leucocytes (× 10^3)</td>
<td>7.9 ± 2.2</td>
<td>7.2 ± 2.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>14.1 ± 1.3</td>
<td>13.9 ± 1.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Platelets (× 10^3)</td>
<td>301.7 ± 73.5</td>
<td>266.0 ± 60.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Physician’s global score</td>
<td>4.6 ± 0.6</td>
<td>1.5 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DAREA</td>
<td>12.9 ± 5.8</td>
<td>2.7 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

First and last visit DAREA were compared using Wilcoxon tests (paired variables). Components of DAREA are in bold.

Fig. 2. Analysis of DAREA in eight patients with REA studied prospectively at the first visit, at an intermediate visit and at the last visit. A consistent improvement of clinical status as indicated by the fall of DAREA was observed in six patients. DAREA correlated well with the physician’s assessment (see Fig. 1B).

Consistent decrease of DAREA over time

The most dynamic direct measures of the acute phase response and studies have shown that CRP is more responsive to tissue injury in comparison with ESR [26]. Moreover, as a protein induced by the action of pro-inflammatory cytokines, CRP responds very rapidly to the influence of inhibitors of such cytokines and much faster than ESR. However, CRP was used in mg/dl rather than g/l in order to prevent an overweight of this laboratory measure in the overall score.

Haemoglobin and leucocyte counts (although also correlating well with the physician’s global assessment) were not included into the final score for two reasons: (i) certain therapeutic measures, such as NSAIDs or glucocorticoids (which are used occasionally in REA) can lead to ‘false’ changes due to toxicity or other unwanted effects (NSAIDs by inducing gastrointestinal blood loss, and glucocorticoids by inducing leucocytosis); (ii) in contrast to the above five variables, haemoglobin and leucocytosis do not constitute part of the established disease activity indices for RA [24] and use of similar variables may allow for ‘harmonization’ of indices or core sets for different disorders and, thus, for better comparability between diseases.

The reasons for choosing the 3-point scale rather than VAS for patients’ assessments were based on several grounds: (i) all these variables correlated very well with the physician’s global assessment and with each other and could therefore be used in an interchanging way; (ii) we wished to obtain an index whose components should bear similar weights, whilst the use of two VAS scales each potentially amounting to 10 cm or 100 mm would put an overweight on patients’ assessments; and (iii) we wished to obtain a score which could be calculated as easily as possible by the physician and be used also at the office level without time constraints.

A simple numerical addition of the individual values allows a DAREA score to be obtained which reflects disease activity. This score has face, content, criterion and construct validity and showed reasonable discrimin-
ant power. In particular, a complete remission was indicated by a DAREA score of \(<1\) (i.e. 0 values for all non-laboratory variables plus normal value for CRP). In fact, remission was observed in 11 of the 23 patients of the prospective part of the study after therapy. Moreover, a progressive decrease of DAREA could be seen in most of the patients analysed at several points in time. Thus, DAREA should allow good discrimination of the efficacy of drugs or placebo in controlled clinical trials. High DAREA scores were seen in patients at initial presentation and a lack of improvement of DAREA was observed in many patients who did not achieve remission. Thus, a lack of improvement of DAREA in long-term follow-up could support the decision to institute a slow-acting disease-modifying drug. However, the use of DAREA will have to be investigated in more detail in order to prove its applicability under these circumstances.

Therapy of REA is currently under debate, and sulphasalazine may not be efficacious [27]. Although in the present study all patients were treated with antibiotics based on previous reports [10, 11] the patients of the cross-sectional group treated with antibiotics fared worse with respect to remissions and particularly the change of DAREA than the patients from the prospective study group (data not shown). Thus, this investigation does not allow any conclusions on the efficacy of antibiotic therapy in REA and does not support that such therapy is efficacious. At present, there is no evidence that antibiotic therapy is beneficial in REA, and any conclusion on therapeutic effects can only come from a prospective, randomized, placebo-controlled clinical trial in a large cohort of patients, which is currently ongoing in Europe. However, DAREA appears to be a useful tool for the evaluation of the results of such a study [28].

Taken together, the results of this investigation indicate that DAREA is a simple and efficient means to assess disease activity in REA. It is easily applicable even in routine clinical settings and seems to be an effective measure for future controlled clinical trials. The selection of its component variables was based on their excellent performance vis-à-vis other groups of variables as well as the similarity to the RA core sets. The latter allows for harmonization and for similar data collection in RA and REA trials. Assessing patients with REA using DAREA may help to determine therapeutic decisions, particularly with regard to long-term treatment in patients with chronic forms of the disease. DAREA is a reliable, valid and reproducible index which is sensitive to change in the assessment of patients with REA and should be tested in further clinical trials. Therefore, we suggest that the variables necessary for the calculation of the DAREA index should be included routinely in the care of and in trials in patients with REA. If it also proves to be valuable in the context of such future trials, it could ultimately become part of a core set for disease assessment in REA to be determined in international consensus finding meetings.

References

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