The assessment of disease activity in rheumatoid arthritis

J.S. Smolen1,2, D. Aletaha1

1Division of Rheumatology, Medical University of Vienna, and 2Hietzing Hospital, Vienna, Austria.
Josef S. Smolen, MD
Daniel Aletaha, MD

Please address correspondence and reprint requests to:
Josef Smolen, MD,
Division of Rheumatology,
Medical University of Vienna,
Vienna A-1090, Austria.
E-mail: josef.smolen@meduniwien.ac.at

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ABSTRACT
Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive damage of diarthrodial joints, with variable extra-articular manifestations. Joint damage begins early in the course of the disease as a consequence of the active inflammation, and can lead to progressive and irreversible disability. Successful treatment relies on patients attaining low disease activity or a state of remission, which have become achievable goals since the improved use of methotrexate (MTX) and the introduction of biological agents, such as tumour necrosis factor (TNF) inhibitors. To allow physicians to evaluate the indication and effect of particular therapies, accurate assessment of disease activity is necessary. Disease states in RA can be evaluated by a number of measures. These include signs and symptoms, such as counts of tender and swollen joints; laboratory measures like the acute phase response, which is a direct reflection of the underlying inflammatory activity; and patient-focused variables to measure pain and global assessment of disease activity. Some of these (and additional) measures are used in composite indices to assess disease activity or a disease activity state at any point in time and can inform the physician (and patient) about improvement (or deterioration) in disease activity from a particular level at baseline, to that seen at any specific time point. The accurate assessment of disease activity is, therefore, an important part of the care of patients with RA. However, it can be complex to perform in the clinical setting, so new and simplified measures have evolved. Next to disease activity, the disease outcome is of utmost importance, in particular disability and quality of life, which are assessed using patient reported questionnaires. Radiographic assessment of structural changes is also an important outcome of RA and mirrors joint damage. The latest developments in the field are discussed and will help to identify patients who can benefit most from today’s opportunities of pharmacotherapy, allowing optimisation of patient care.

Characteristics of rheumatoid arthritis
Rheumatoid arthritis (RA) is the most common chronic inflammatory joint disease, is a major cause of disability, and is associated with increased comorbidities and mortality (1-4). It is characterised by pain, swelling, and progressive damage of synovial joints, most commonly the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints, as well as those of the wrists and knees (5, 6). RA has a large range of articular and peri-articular manifestations, including tenderness to palpation, morning stiffness, and severe motion impairment in the involved joints, and tenosynovitis. The clinical presentation of disease varies, but pain with symmetric swelling of small joints is the most frequent finding, and fatigue, weight loss, and malaise are also common clinical signs. In addition to these physical signs and symptoms, several laboratory abnormalities can be detected. The activation of the acute phase response can be seen by increases in the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. ESR and CRP levels, as well as joint counts, are correlated with radiographic changes, both when measured cumulatively over time (7-10) as well as at the beginning of a therapeutic course (10). In addition, as an auto-immune disease, auto-antibodies, such as rheumatoid factor (RF), anti-citrullinated peptide antibodies and anti-RA33 (a nuclear antigen), are likely involved in the pathogenesis of the disease (1, 11) and assist in the classification, diagnosis and prognostication of RA. Many of these characteristics are included in the American College of Rheumatology (ACR) criteria which

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are used to classify the disease (12). These criteria, which include joint damage (erosions) and rheumatoid nodules, were derived from patients with established RA, and thus may not be useful for patients with early disease (13). Indeed, new classification criteria for early disease are currently in development by the European League Against Rheumatism (EULAR) and the ACR.

Joint inflammation in RA is initiated and perpetuated by the migration, activation, and retention of inflammatory cells in the synovial membrane, including T cells, B cells, plasma cells, dendritic cells, macrophages and mast cells (Fig. 1). Angiogenesis also occurs, and the synovial lining becomes hyperplastic. A plethora of pro-inflammatory molecules is also produced, including inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumour necrosis factor-alpha (TNF-α), which stimulate the production of various additional mediators of inflammation and tissue destruction, including prostaglandins and matrix metalloproteinases. The latter are enzymes that can degrade components of the extra-cellular matrix and are primarily responsible for cartilage damage (14, 15). While the primary cell types involved in cartilage damage are chondrocytes, the progressive destruction of bone that is characteristic of the disease is mediated by osteoclasts (14, 16-18). Different factors have been associated in osteoclast differentiation and maturation, including the receptor activator of NF-κB ligand (RANKL) and its receptor (RANK) as well as the pro-inflammatory cytokines mentioned above; activation of the transcription factor AP-1 is essential in this process (19-24).

Although joint damage generally begins early in the course of RA (25, 26), as also evidenced in experimental models (27), the link between damage and disability is strongest in late disease (28, 29). Indeed, joint damage accounts for approximately one quarter of disability in long-standing disease (30-32). While effective treatment inhibits the progression of joint damage, full reversion of joint damage is currently unachievable. Thus, there are both reversible (those due to current disease activity) and irreversible (resulting from accrued damage) components in functional limitation that can contribute to RA disability (31, 33). However, there may be prospects to induce healing of bone lesions by activating osteoblasts in conjunction with inhibiting inflammation (34). If this becomes clinical reality, one could test the reversibility of the damage-associated component of disability.

**Assessment of disease activity**

In order to optimise therapy and patient outcomes, accurate assessment of disease activity is required. The best outcome for patients (low disease activity or remission) can be obtained by adhering to an algorithm combining optimal treatment with the most appropriate assessment of outcome (35), and switching therapies rapidly if the desired result is not attained (33, 35) (Fig. 2). Whilst aiming at low disease activity with intensive monitoring and...
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Rapid dose adjustments is an effective therapeutic path (36, 37), a state of remission offers the greatest benefits to patients (38-40). There are a number of measures that are used to assess disease activity in RA, including the Disease Activity Score (DAS), the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index (RADAI), and their derivatives (41-46). The DAS was developed by van der Heijde and colleagues in Nijmegen, The Netherlands, in the 1990s as a tool to measure disease activity in patients with RA (41). It comprises the following components: the Ritchie articular index, number of swollen joints (based on 44 joints), ESR (or subsequently also CRP), and a measure of general health (GH) status based on a visual analogue scale (VAS). A modified version of the DAS, the DAS28, uses a non-graded 28-joint count on both swollen and tender joints in place of the Ritchie articular index and 44-joint count used in the DAS (47) (Table I). The joints assessed in the 28-joint count are the shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and the knees (6, 48) (Fig. 3). The DAS28 level indicates the actual (or current) activity of RA disease on a scale of about 1-9, has validated disease activity category cut-off points (Table II), and is derived as follows:

$$\text{DAS28} = 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$$

Number of tender and swollen joints using 28-joint counts (TJC28 and SJC28); ESR in mm/h; patient’s GH or global disease activity on a 100 mm VAS.

It is clear from the DAS28 formula that the tender joint count (TJC) is weighted twice as highly as the swollen joint count (SJC), and Bakker and colleagues have noted that the ESR in the DAS28 formula is also highly weighted (49) as depicted in Fig. 4A and B, which show the contributions of each individual variable: tender joints (0.56 x \sqrt(TJC28)), swollen joints (0.28 x \sqrt(SJC28)), ESR (0.70 x ln(ESR)) and patient global assessment (0.014 x GH) to the DAS28. The graphs reveal that ESR, even when amounting to 20 mm/h, which is within the normal range, accounts for 2 points on the DAS28 scale. This is more than the contribution of the maximum possible global health score (i.e. 100/100 mm on the VAS), or of the maximum number of swollen joints (i.e. 28/28 assessed joints). Moreover, the steepest portion of the curve for ESR is within the normal range. Thus, the relative contribution of swollen joints and patient global assessment to the total DAS28 is quite low. While the weighting system for the DAS and DAS28 were derived from actual changes in treatment on patients in clinical practice (41, 47), these weights apparently do not sufficiently account for actual contributions of the variables to the outcome of RA. This is particularly true when remission is evaluated which was a virtually unreachable state when these scores were developed.

Other physician-led composite measures of disease activity include the SDAI and the CDAI, which are simplified measures that are easier to use. The SDAI requires a simple numerical summation of five traditional core set variables: swollen and TJC's (using the same 28 joints that are scored in the

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Table I. Measures included in the disease activity assessment scores.

<table>
<thead>
<tr>
<th>Measure</th>
<th>DAS28</th>
<th>SDAI</th>
<th>CDAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SJC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Physician’s/Evaluator’s global assessment</td>
<td>–</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ESR or CRP</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Patient’s global assessment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

TJC, tender joint count; SJC, swollen joint count.
DAS28), evaluator’s and patient’s global assessments of disease activity (in cm VAS), and CRP levels (in mg/dL) (Table I) (44, 45), but is equally as valid. These composite indices are derived as follows:

SDAI = SJC28+TJC28+EGA+PGA+CRP
CDAI = SJC28+TJC28+EGA+PGA+CRP

Both the SDAI and CDAI have been validated (46, 50, 51), and both also have documented/validated cut-off points for categories of disease activity (high, moderate, low, and remission) which are highly correlated with the degree of joint damage (39, 52, 53) (Table II). The SDAI and CDAI strongly correlate with the DAS28, and, like the DAS28, moderately correlate with Health Assessment Questionnaire-Disability Index (HAQ-DI) and radiographic score (39, 44, 52, 53) as well as with CRP and ESR levels (9).

The RADAI is a measure of patient-perceived disease activity and does not include physician or laboratory measures (42, 43). It is intended to complement the physician-led indices, or be used when physicians are too reluctant to perform joint counts in their offices. Most patients can complete the RADAI questionnaire in 5-7 minutes. The five-item individual scores are: recent disease activity, current disease activity, arthritis pain, morning stiffness, and joint tenderness. The first three items are scored on ranges of 0-10 on anchored numerical rating scales. Morning stiffness is scored on a categorical range of 0-6 (e.g. 0=no morning stiffness; 6=morning stiffness that lasted all day), and joint tenderness is similarly scored on a range of 0-48, with a range of 0-6 for each of the joint categories (e.g. 0=no pain in each of the shoulders, elbows, wrists, fingers, hips, knees, ankles, and toes; 48=severe pain in all of these joints). The scores for the last two items are transformed to the same 0–10 scale as the first three items. If all the items are answered, the values are added and then divided by the number of items to provide a single total RADAI score between 1 and 10 (see derivation below).

RADAI = (recent disease activity + current disease activity + arthritis pain + morning stiffness + joint pain)/N

N: number of items scored

Thus, various computations are needed and require the use of a calculator, and often time of the physician, which could be spent on examining joints, the organ the rheumatologist should focus on, examining the way a cardiologist would examine the heart and not leave it to the patient.

All of these indices provide an accurate assessment of disease activity in patients with high-to-moderate RA disease activity. However, when remission is addressed, the SDAI and CDAI are more stringent than the DAS28, since the latter allows for more than 10 residual swollen joints in its classification of remission (53-55). Indeed, the differential weighting of TJC and SJC in the DAS28, in contrast to their unweighted nature in the SDAI and CDAI, results in some peculiar differences in the classification of remission by DAS28 and SDAI/CDAI (Fig. 5). Moreover, remission rates by DAS28 can sometimes exceed ACR70 response rates, and occasionally even ACR50 response rates (Table III), an observation which highly reduces the face validity of calling DAS28 remission really “remission”, despite the fact that it clearly constitutes a state of appreciably low disease activity. In contrast to DAS28 remission, SDAI and CDAI defined remission, by virtue of the construction of the indices, cannot exceed one swollen plus one tender joint, or two of either with none of the other. Last, but not least, the SDAI and CDAI are the only scores which do not require a calculator or computer.

While the above measures are valuable for assessing disease activity, they neither measure physical function nor provide an estimate of the degree of joint damage; other measures are used to assess these outcomes. Importantly, however, there is a correlation between worse disease/higher disease activity and poorer physical function/greater disability. Functional and radiographic outcomes differ between patients...
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depending on the disease activity category they attain, even if the same proportional response (change from baseline) is achieved (40). In patients who attain the same disease activity category, physical function, and radiographic progression may not differ significantly with different degrees of response. As a result, assessment of the response level and attained state of disease activity should both be included in clinical trial reporting (61, 62), and also in assessment of RA in daily practice. In general composite indices more accurately reflect the overall state of the disease than individual measurements (63-66).

Table III. Comparison of DAS28 remission with ACR50 and ACR70 scores in selected clinical trials of biological agents for RA. Note that in most instances DAS28 remission rates exceed ACR70 and sometimes even ACR50 response rates.

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Time point</th>
<th>Treatment</th>
<th>DAS28 remission (&lt;2.6) (%)</th>
<th>ACR70 (%)</th>
<th>ACR50 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early RA</td>
<td>Week 52</td>
<td>ETN + MTX (n=274)</td>
<td>50</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MTX alone (n=268)</td>
<td>28</td>
<td>28</td>
<td>49</td>
</tr>
<tr>
<td>Late RA</td>
<td>Week 24</td>
<td>GOL 50 mg (n=153)</td>
<td>10</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GOL 100 mg (n=153)</td>
<td>16</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (n=155)</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>GOL 50 mg + MTX (n=89)</td>
<td>20</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GOL 100 mg + MTX (n=89)</td>
<td>22</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MTX alone (n=138)</td>
<td>6</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GOL alone (100 mg) (n=133)</td>
<td>12</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>TCZ 4 mg/kg (n=213)</td>
<td>13</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCZ 8 mg/kg (n=205)</td>
<td>27</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (n=204)</td>
<td>1</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>TCZ 4 mg/kg + MTX (n=161)</td>
<td>8</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCZ 8 mg/kg + MTX (n=170)</td>
<td>30</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + MTX (n=158)</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

ETN: etanercept; GOL: golimumab; TCZ: tocilizumab.

Disease activity and physical function

The ACR core set of disease activity measures comprises physical function (67), as assessed by the health-assessment questionnaire-disability index (HAQ-DI) (68). In contrast, the EULAR core set does not include assessment of physical function (69). This is a consequence of differing views as to whether disability constitutes an activity or an outcome measure. While there is no absolute truth in this debate, we regard measures of disease activity as reflecting events that are fully reversible once inflammation is abolished, while we define measures representing potentially irreversible characteristics of the disease as outcome variables. In this context the term outcome is seen as a result of the disease and the processes leading to this outcome and has to be distinguished from the term endpoint (such as in clinical trials).

Disability is mainly related to pain, tenderness and stiffness of the joints (8). Indeed, it has been clearly shown that in early phases of RA disability is highly related to disease activity and stringent remission can fully reverse it (28, 31); in late stages, however, disability is governed by both disease activity and joint damage and even in stringent remission disability will be partly irreversible. These notions relate to the group level, while in individual patients they will relate to the type of joint damage (much damage in one or two vs very little in many; large vs small joint, etc).

We have recently suggested expanding the concept of disability to reversible and irreversible components as well as to disease activity-related (ACT-HAQ) and joint damage-related (DAM-HAQ) components (31, 70). This concept is depicted schematically in Fig. 6A and B. Both figures show the compression of the ACT-HAQ by the DAM-HAQ with increasing disease duration and/or joint damage, since these components are not additive as can be seen by comparing baseline data from clinical trials of the same compounds in patients with early- and long-standing disease: these show similar HAQ and DAS28 values. In Fig. 6A the change in the floor of
physiological function that can be reached by maximal reduction of disease activity is additionally shown to rise with increasing joint damage or disease duration. Indeed, the responsiveness of the HAQ to active medication decreases with duration of RA, becoming indistinguishable from that of placebo in long-standing RA (71). The contribution of joint damage to the HAQ has now been quantified (70). In Fig. 6B the compression of the ACT-HAQ by the DAM-HAQ is depicted in a different way which also reveals that there are other components (green) contributing to the reversible as well as the irreversible part of the HAQ. These may include many other factors which affect physical function, such as psychological factors or concomitant diseases. Thus, patient centered instruments on physical function or quality of life have to be seen contextually and the potential complexity just described borne in mind.

**Challenges in clinical practice**

Although accurate assessment of RA disease activity is one of the most important aspects of caring for patients with RA, conducting the assessments can be complex in the clinical setting (46, 72). The formula to calculate the DAS28 score is complicated, requiring the use of a calculator or computer program. The need to transform scores for morning stiffness and joint tenderness in the RADAI score means that the total RADAI score also needs to be electronically calculated. The simplified measures (i.e., the SDAI and CDAI) perform at least as well as the complex indices to evaluate disease activity and response to treatment, are easier to calculate, and more stringent in the definition of remission. These assessment measures are important in routine practice as they allow physicians to evaluate the success (or otherwise) of therapy by determining whether patients have achieved low disease activity or remission, and to adapt therapy as required in order to attain these goals (73). It is also important that patients are aware of their "DAI" score, just as it is important for diabetic patients to know their HbA1c levels; with this information at hand, patients can relate the scores to the level of their disease activity, as assessed by their rheumatologist, and can relate changes to all aspects of their disease. A joint count is the most specific measure to assess RA disease activity, is key to measuring outcomes in clinical trials, and is incorporated into most disease activity instruments. Assessing joints is important because the synovial membrane is the key tissue affected by the RA disease process, and because SJC are significantly associated with subsequent joint destruction; on the other hand, TJC are also highly correlated with disability (8, 74). To obtain the most accurate results, joint counts should be performed by the same trained observer at each visit. However, despite training to increase recognition of swollen and tender joints and increase reliability and sensitivity of measurement, there is still variability among observers in determining the number of swollen and number of tender joints (75). This is not restricted to rheumatology, of course; variability in assessments is common to other therapeutic areas, such as blood pressure monitoring (76).

Of the other measures, laboratory tests are helpful as general indicators of inflammation, even though the most commonly assessed biomarkers – ESR and CRP – are normal in 40% of patients at presentation. CRP and ESR (with the limitations discussed above), along with RF, are still the only measures that are routinely used and useful (77), despite much research to find other reliable prognostic biomarkers for severe disease. Finally, patient questionnaire scores may improve due to factors unrelated to RA and, as with any questionnaire, they may be affected by cultural variability and can be manipulated by patients to give perceived “desired” results (72).

**Using disease activity measures to optimise therapy**

A number of studies have been conducted to identify prognostic factors for use in strategic algorithms to optimise therapy for patients with RA. One study was conducted in 204 patients to determine which disease activity variables for RA were associated with a change in therapy in clinical practice (50). The most important variable was SJC, followed by morning stiffness, CRP, TJC, and patient global assessment. In terms of composite measures, the SDAI was found to be more discriminating than the DAS28 (using either measures of CRP or ESR). Furthermore, of all the variables studied (including the DAS28), the SDAI most closely correlated with the physicians’ decisions to change therapy. This was further confirmed in an ACR initiative spearheaded by Felson, which showed that among numerous tools and their variations, the decisions to change therapy were best associated with changes in SDAI and CDAI (51).

In a larger analysis of data from 1,905 patients collected over 25 years, changes in the DAS set of variables indicat-
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The relationship between the rapid response seen with certolizumab pegol therapy and long-term outcomes (83, 84). Patients who had improvements in DAS28 of ≥1.2 at week 12 had a higher probability of having low disease activity/remission at 1 year than patients with a DAS28 decrease of <1.2 at week 12 (85). Furthermore, patients who achieved a rapid response to treatment with certolizumab pegol (i.e. a change in baseline DAS28 score ≥1.2 at week 6) had a higher probability of achieving better outcomes, including higher ACR20, ACR50, and ACR70 responses and greater improvements in pain, physician function and fatigue, at 1 year than patients not achieving this response until week 12 (84).

Decision trees can also be used to identify baseline factors that could be predictive of patients who are likely to have rapid or slow progression of radiographic damage, more or less disability, and a better or worse disease course. In a 5-year study of 191 patients, radiologic damage and improvements in HAQ score were predicted by baseline HAQ score, Ritchie index, ESR, CRP levels, and presence (or absence) of erosions (85). In a longer-term study, of 112 patients over 12 years, disease progression could be predicted at the individual patient level using decision trees that incorporated baseline RF positivity, HAQ score, SJC, and the presence of erosions (86). Similarly, Classification and Regression Tree (CART) analysis has been used to determine factors early in the course of therapy that could be predictive of long-term outcomes. Most recently, the prognostic significance of a combination of clinical and related laboratory data measured at baseline and within the first 12 weeks of therapy with certolizumab pegol has been evaluated for the ability to predict low disease activity (DAS28 score ≤3.2) at 1 year (87). The empiric models derived using CART accurately classified approximately 75% of RA patients as responders or non-responders to certolizumab pegol treatment (based on DAS28 scores at week 52) within the first 12 weeks of initiating therapy. Similar results were achieved when CDAI was used instead of DAS28 to predict response at week 52 from week 12 results (81). All of these observations are fully in line with previous findings which have been detailed above (81).

Prognostic algorithms can also be constructed to assist in the clinical setting, to identify patients in the first year of RA who are likely to have poor function by 5 years, and who could benefit from aggressive drug therapy. In a study of 985 patients, functional grade III/IV and HAQ score at 1 year were the most important predictors of functional outcome (88). The DAS28 score also predicted functional outcomes, although to a lesser extent than functional grade III/IV and HAQ scores. This is likely due to the fact that grade III/IV RA, after the introduction of a disease-modifying anti-rheumatic drug (DMARD) or biological therapy, already reflects irreversible joint damage to a large extent, and so does a high HAQ score in patients with long-standing disease, while DAS 28 is “only” a measure of reversible disease activity (31). Other variables tested, which were not predictive of outcome, were socioeconomic status, hemoglobin levels, and radiographic status. Finally, combining swollen joint counts, CRP and RF into a matrix model allows prediction of the risk of rapid radiographic progression (89).

Thus, while disease activity assessments can be used to identify patients who are not responding to treatment and require a change in therapy, or those at risk of rapid disease progression, better prognostic factors are generally needed. However, at the present time, disease activity at any time point, but especially over time, is still the best predictor and thus best marker of outcome in RA (77).

Summary

In conclusion, assessments of disease are useful when following patients through their treatment course, despite some limitations to their applicability in routine clinical practice. Composite disease activity indices have special merits in providing a wide range of information, correlating with physical function and joint damage, allowing tighter control of therapy, and supporting the optimisation of treatment on an
individual patient basis. The advent of the TNF inhibitors for the treatment of RA, including the most recently approved agent in the class, certolizumab pegol, and other biological agents, have made low disease activity and remission a reality for many patients with RA. Predictive treatment algorithms encompassing all of the aspects of disease activity will allow these ambitious goals of therapy to be achieved (90). To this end, finding additional markers that can more accurately predict therapeutic response and long-term outcomes will be a crucial step in optimizing treatment algorithms (77). However, already now it is possible to predict outcomes using validated assessments, allowing further (and complete) optimization of care throughout the course of disease.

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