Rheumatoid arthritis disease measurement: a new old idea

Kathryn F. Hobbs¹,² and Marc D. Cohen¹,³

Abstract

In many medical treatment areas, the use of treatment targets has led to improved outcomes, including a reduction in end-organ damage. In rheumatology, appropriate targets appear elusive, although preventing joint damage, minimizing disability and improving mortality are end results on which most clinicians would agree. Sophisticated measures of disease activity, particularly in early disease, have only recently been objectively evaluated. Swollen joint count, tender joint count, acute-phase reactants, citrullinated antibody titres (ACPAs), patient and physician assessment of disease activity, radiographs and other imaging modalities such as US and MRI may all be appropriate to measure. A number of composite measures have been proposed as possible or practical methods for defining RA disease activity. Some require testing of acute-phase reactants, but several do not. ACR20/50/70 scores are useful for measuring change from visit to visit, while others (DAS28, HAQ, Simplified Disease Activity Index, Clinical Disease Activity Index and Routine Assessment of Patient Index Data) assess disease activity at a single point. Disease measures have now been used in myriad clinical trials and studies. The FIN-RACo, TICORA, CAMERA and BeSt trials employed measures of disease activity at predetermined points to guide treatment decisions. These trials supported the consistent use of objective measures to derive significant benefits from treat-to-target strategies. The concept that objective measures can guide aggressive treatment to reach a defined optimal end point or target is a strategy that rheumatologists hopefully might now agree is critically important.

Key words: rheumatoid arthritis, measures of disease activity, ACR20/50/70 scores, DAS28, HAQ, SDAI, CDAI, RAPID.

Introduction

In specialties of medicine other than rheumatology, the use of treatment targets leads to improved outcomes, usually a reduction in end-organ damage [1–3]. These targets have wide acceptance, and physicians regularly and routinely order blood glucose and HbA1c levels, cholesterol and triglyceride tests, and measure blood pressure. Therapy is then based on these determinations and changed until targets are reached. Moreover, these targets are usually understood by patients, at least to some degree, and many patients participate in this process of achieving treatment goals.

Rheumatology, at least in the USA, has been somewhat slow to identify and accept the treat-to-target paradigm. Although many of the immunological processes in RA are known, they are complicated, and different facets may not be equally important in individual patients. Appropriate targets seem elusive, although preventing joint damage, minimizing disability and improving mortality are end results that would be universally appreciated [4–7]. Several composite and increasingly sophisticated measures of disease activity have been objectively evaluated over the last two decades. Swollen joint count (SJC), tender joint count (TJC), acute-phase reactants, citrullinated antibody titres, patient and physician assessment of disease activity, radiographs and other imaging modalities such as US and MRI may all be appropriate to measure. It is likely that no single variable is sufficient, and that some calculus of these values may be necessary to adequately describe rheumatoid disease activity [8–12]. The heterogeneity...
and complexity of these measures, as well as their perceived expense in time, effort and money, contribute to some reluctance by rheumatologists, especially in the USA, to perform them regularly and to change treatments accordingly. The routine, successful use of composite measures of disease activity has been much more commonplace in Europe and other parts of the world for many years.

What to measure

RA disease measurement has evolved slowly over time, and a large number of factors have contributed to this. Composite measures have been proposed and verified in a number of thoughtful studies [13–21]. In clinical trials, early treatment has led to improved outcomes, particularly less joint damage and better function [22–28]. New medications, especially sophisticated biologics, have been licensed internationally. Their use has led to outcomes, previously thought to be unattainable, to the point where the concepts of remission and repair now seem possible [22–28]. However, these drugs are expensive, and this has resulted in pressure for physicians to use these drugs only in selected patients for whom there is considerable evidence that they might be effective. Soon, third-party payors will likely require documentation of the efficacy of these drugs in individual patients longitudinally. In addition, treat-to-target trials have accomplished better outcomes than have routine or traditional treatments [29–35]. All of these concepts have changed the clinical practice of rheumatology and elevated expectations, and all are based on objective disease measurements. The importance of measuring actual disease activity as well as patient improvement has been stressed by other researchers [13–21]. Optimal therapeutic strategies have yet to be determined, but the achievement of the lowest disease activity and its measurement seem intuitively essential to discover the best treatment practices.

An international task force suggested a variety of recommendations regarding the modern treatment of RA [35]. They also evaluated the available evidence supporting each of their recommendations. As overriding principles, they agreed that (i) the treatment of RA must be based on shared decision making between the rheumatologist and the patient; (ii) the goal of RA treatment is to maximize long-term health-related quality of life by controlling symptoms, prevention of structural damage and normalization of function; (iii) abrogation of inflammation is critical and (iv) treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes. The 10 final published recommendations on treating RA to target achieved through consensus are found in Table 1 [35].

These recommendations specifically define the treatment target for RA and how therapy should be modified to attain the target and sustain the response. Disease activity measures are essential to achieving the treatment goals. The evidence supporting these recommendations is worth examining.

A number of composite measures have been suggested as possible and sometimes practical methods for defining RA disease activity [13–21]. Some of these are listed below with their constituent parts (Table 2 and Fig. 1) [36–42]. Some require laboratory testing of acute-phase reactants, but several do not. Some emphasize patient-reported outcomes, but the weight given to this variable is not consistent. The ACR 20/50/70 measurement is a categorical tool, whereas the others are more continuous measurements [20]. While the HAQ allows the concept of some disease non-reversibility based on significant radiographic change and loss of function, the other tools do not. None of them weighs the importance of which joints are involved. None of them includes any quantification or contribution of imaging results, despite the fact that both US and MRI are often more sensitive and specific modalities than clinical or laboratory evaluations. The

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**Table 1** Recommendations on treating RA to target [35]

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>The primary target for treatment of RA should be a state of clinical remission.</td>
</tr>
<tr>
<td>Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.</td>
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<tr>
<td>Although remission should be a clear target that is based on available evidence, low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.</td>
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<tr>
<td>Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.</td>
</tr>
<tr>
<td>Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.</td>
</tr>
<tr>
<td>The use of validated composite measures of disease activity that include joint assessments is needed in routine clinical practice to guide treatment decisions.</td>
</tr>
<tr>
<td>Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.</td>
</tr>
<tr>
<td>The desired treatment target should be maintained throughout the remaining course of the disease.</td>
</tr>
<tr>
<td>The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors and drug-related risks.</td>
</tr>
<tr>
<td>The patient should be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.</td>
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The accuracy of clinical SJC and TJC assessments has issues of reproducibility and may not differentiate between tender joints in FM and the swelling of OA, fibrous thickening or obesity. Patient assessments may be confused by comorbid symptoms and fluctuations of mood. The ACR20/50/70 has been correlated with the 28-joint DAS (DAS28) and HAQ, but the former is a measurement of change. The DAS28, HAQ, Simplified Disease Activity Index, Clinical Disease Activity Index and Routine Assessment of Patient Index data have been highly correlated with each other, as have DAS assessments in an individual patient from one treatment to another [23/28]. Many have specific end points to define remission and low, moderate and high disease activity [23–28]. Many have been used in clinical trials, with government licensing groups often requiring significant changes in ACR20/50/70, DAS28 and HAQ measurements for product approval. Rather than dictate which tool should be used by whom, the emphasis has been the consistent use of an assessment tool, with treatment changes tied directly to the results.

Because of some of the difficulties inherent in these measures of disease activity, there has been intense interest in using the laboratory to find combinations of immunological and enzymic variables and biomarkers that might be useful for following RA and its treatment. It seems unlikely that a single marker would be able to capture the complexity of pathways involved in RA, but combinations of markers might reflect various critical aspects that could then be integrated into a single commercially available test. Hypothetically these tests would be more objective, without any of the subjectivity inherent in clinical judgements by physicians and patients. Multibiomarker tests could at least complement clinical disease activity measures. They might better mirror the complex pathophysiology of RA across the heterogeneity of patients with RA disease measurement.

**TABLE 2** Outcome measures in RA [36–41]

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>ACR20/50/70</th>
<th>DAS28</th>
<th>SDAI</th>
<th>CDAI</th>
<th>GAS</th>
<th>ERAM</th>
<th>RADAI</th>
<th>RADARA</th>
<th>RAPID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient function</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Patient pain</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
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<td></td>
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<tr>
<td>Patient global</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Physician global</td>
<td>+</td>
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<td>+</td>
<td></td>
<td></td>
<td>+</td>
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<td></td>
<td></td>
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<tr>
<td>No. of tender joints</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>No. of swollen joints</td>
<td>+</td>
<td></td>
<td>+</td>
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<td></td>
<td>+</td>
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<tr>
<td>ESR or CRP</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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</table>

CDAI: Clinical Disease Activity Index; ERAM: Easy Rheumatoid Arthritis Measure; GAS: Global Arthritis Score; RADARA: Real-time Assessment of Disease Activity in Rheumatoid Arthritis; RADAI: Rheumatoid Arthritis Disease Activity Index; RAPID, Routine Assessment of Patient Index Data.

**FIG. 1** Clinical measurement tools to guide treatment decisions [36, 42].

<table>
<thead>
<tr>
<th>Remission</th>
<th>Low Disease Activity</th>
<th>Moderate Disease Activity</th>
<th>High Disease Activity</th>
</tr>
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<tbody>
<tr>
<td>SDAI ≤3.3</td>
<td>3.4-11</td>
<td>12-26</td>
<td>&gt;26</td>
</tr>
<tr>
<td>CDAI ≤2.8</td>
<td>2.9-10</td>
<td>11-22</td>
<td>&gt;22</td>
</tr>
<tr>
<td>GAS ≤3.3</td>
<td>4-7</td>
<td>8-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>DAS28 &lt; 2.6</td>
<td>&lt;3.2</td>
<td>N/A</td>
<td>&gt;5.1</td>
</tr>
<tr>
<td>RAPID &lt; 3.0</td>
<td>&lt;6</td>
<td>26 and ≤12</td>
<td>&gt;12</td>
</tr>
</tbody>
</table>

CDAI: Clinical Disease Activity Index; GAS: Global Arthritis Score; NA: not available; RAPID: Routine Assessment of Patient Index Data; SDAI: Simplified Disease Activity Index.
RA, provide a quantified score, ultimately be easy and inexpensive to use and eliminate interphysician variability inherent in joint and radiograph measurement. For now, useful biomarkers are not available.

There has been progress, however, in developing these previously hypothetical biomarkers, although the process is often quite complicated [43–46]. Biomarker possibilities are often derived from gene expression and protein array analyses and bio-informatic databank searches. Clinical trials are necessary to determine which of the biomarkers are most strongly correlated with RA disease activity across different cohorts and which contribute most strongly to prototype algorithms. The biomarker assays must be precisely accurate and reproducible; the algorithms should be tested from multiple sites and across heterogeneous disease types and verified repeatedly as useful in independent RA patient groups. Examples of potentially useful biomarkers that may correlate with the different facets of RA pathophysiology include cytokines, receptors, adhesion molecules, growth factors, metalloproteinases, hormones, acute-phase reactants, chemokines and apolipoproteins. The selected biomarkers must be used in combinations in which each contributes strongly to the algorithm. Each biomarker might be differentially weighted to optimize the algorithm. Recently an example of such a biomarker set included vascular cell adhesion factor-1, epithelial growth factor, vascular endothelial growth factor A, IL-6, type 1 TNF receptor, MMP-1, MMP-3, YKL-40, leptin, resistin, serum amyloid and CRP. This produced a biomarker score that was strongly associated with continuous disease activity measures in seropositive and seronegative patients, in low vs moderate vs high disease activity levels, and appeared to be an accurate correlate with treated disease activity over time [45–49]. Further studies are awaited on these and other types of biomarker groups.

What to do with what is measured

The concept that earlier treatment of RA leads to better outcomes than does delayed treatment seems intuitively obvious, but this too has undergone evaluation and validation in several clinical trials. Studies of early treatment in patients with combination disease-modifying agents and subsequent studies of biologic agents plus MTX resulted in particularly impressive results. In the prebiologic era, the seminal paper by Lard et al. [50] showed that disease activity and radiographic progression were more advanced in those patients in whom treatment was delayed by only 4 months. The article by Nell et al. [51] demonstrated a clinical benefit in those patients with early RA who were treated early in their disease course.

In the biologic era, for patients with early disease, the combination of a biologic and MTX was significantly more efficacious for almost every clinical and radiographical outcome measured compared with treatment with placebo. This was initially established for early RA patients treated with MTX plus TNF inhibitors [26–28]. This construct has subsequently been used successfully for other studies of patients with early RA using combination DMARDs and other biologics such as abatacept, rituximab, tocilizumab and newer drugs under development [52, 53].

Critically, in several of these trials there was a group of responding patients whose disease seemed to resolve with combination therapy, as if very early and aggressive therapy might alter the natural history of the disease. This raised the possibility of remission in early RA.

In fact, remission is now an attainable goal in RA, particularly in those patients with early disease [22–28]. The COMET trial by Emory et al. [54] used remission as a primary end point and demonstrated that etanercept plus MTX was almost twice as likely to achieve remission as was MTX monotherapy (MTX plus placebo) in patients with early, active, moderate to severe RA. Subsequent clinical trials have also used remission as a viable end point, usually evaluating the percentage of patients achieving remission when treated by a particular therapy [55]. Once achieved, remission must be sustained to accomplish maximal effects, such as the abrogation of symptoms, cessation of radiographic damage and no loss of physical function. Future trials using remission as an end point and perhaps directly comparing therapeutic regimens would be extremely interesting.

The evidence supporting the concept of treat to target as a superior therapeutic strategy is mainly from four published trials. The earliest was the FIN-RACo (Finnish RA Combination Therapy) trial, which included 195 patients from 1993 to 1995 [29]. The trial was randomized but with an open parallel-group design. The effects of combination DMARD therapy were compared with monotherapy in patients with early RA. In each patient, therapy was intensified after 3 months in the combination group if <50% improvement was seen in any two of the following: SJC, TJC, CRP level or ESR. In the monotherapy group, treatment was intensified at 6 months if there was <25% improvement in the same set of variables. The goal of the trial was to induce both a DAS28 remission and the original ACR-defined remission. At 2 years, more patients in the combination group achieved remission than in the monotherapy group (37% vs 18%, respectively; \(P = 0.03\)). This study concluded that tighter control of RA disease activity, using the goal of remission in early RA, was superior with combination therapy than with monotherapy. The use of different therapies in the two groups probably makes the contrast between the two forms of tight control less obvious.

The landmark TICORA (Tight Control for Rheumatoid Arthritis) trial did not exclusively use patients with early RA [30]. The trial was randomized but single-blind in design. It included 110 patients from 1999 to 2001 randomized to intensive management with protocol-based escalation of DMARDs or to routine care over 18 months. The intensive management group was seen monthly and the intensity of treatment was increased if low disease activity (DAS44 <2.4) was not attained. The routine group was seen every 3 months and medication changed depending on the clinical judgement of the attending rheumatologist. Compared with routine care, the patients in the intensive management group accomplished a mean
change in DAS44 of −3.5 vs −1.9, a good clinical response in 82% vs 44%, and DAS44 remission in 65% vs 16% (P < 0.001 for each). Radiographic disease progression was less in the intensive management group, with median Sharp scores of 4.5 vs 8.5. This study predated biologics, so the radiographic progression seen in the intensive management group was probably not surprising. The treatment protocol for the intensive management group started with SSZ but progressed to triple therapy with SSZ, MTX, and HCQ, and ultimately through seven steps to ciclosporin and MTX. More medication changes, higher doses of MTX and more IA CSs were given in the intensive management group. The conclusion was that the hypothesis of tight control of RA using intensive, protocol-driven treatment leads to the achievement of targeted outcomes significantly more often than does a routine, subjective treatment approach. This study is probably the most commonly cited in support of the treat-to-target approach for RA.

The CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) trial compared the same treatment in a tight control vs a routine management design [31]. Two hundred and ninety-nine patients with early RA between 1999 and 2003 were randomly assigned to an intensive group that used a computer decision model (SJC, TJC, ESR and visual analogue scale for patient well-being) to evaluate patient status and dictate treatment changes on a monthly basis or to a conventional group where every 3 months they were evaluated by a rheumatologist who decided on treatment changes. In the intensive group, if a 20% improvement was not achieved, treatment was increased until remission was attained (defined as SJC = 0 and two of the following: TJC < 3, ESR < 20 mm/h, visual analogue scale well-being < 20 mm). Treatment began in both groups with MTX and progressed through defined increases in MTX until ciclosporin was added. At 2 years, 50% of the intensive group vs 37% of the conventional group were in remission for > 6 months (P = 0.029). This study used its own unusual definition of remission and the use of a programmed computer-based evaluation and treatment paradigm. The reported outcomes were somewhat similar between the two groups. Nonetheless, this did not preclude the conclusion that an intensive treat-to-target strategy is superior to conventional practice.

The BeSt (Behandel Strategieen) trial included 508 patients with early RA between 2000 and 2002, who were randomized to four treatment protocols: sequential monotherapy, step-up combination therapy and initial combination therapy using either high-dose prednisone or infliximab [32]. Each arm had a number of different treatment steps. Within the groups, predefined treatment changes were made every 3 months using DAS44 measurements with a target of 2.4. If the DAS44 was < 2.4 for > 6 months, then treatment was tapered to the protocol maintenance dose (most often MTX 10 mg/week). Other outcomes measured included radiographic damage, physical function and remission (DAS44 < 1.6). Although the combination groups experienced faster improvement at year 1 of the study, by year 2, there were no statistically significant differences between any of the groups regarding the number of patients in remission. Differences in the other outcomes were relatively modest, even after 5 years of study. This intensive regimen did allow a large number of patients to discontinue all medications (23%), if only temporarily [56]. Although there have been many conclusions derived from this study, there is clear evidence to support the concept of using available measures to treat to target as a means of accomplishing clinical remission and radiographic slowing [57].

**Conclusion**

The use of objective measures to guide aggressive treatment to reach a defined target is an effective strategy about which rheumatology experts can almost unanimously agree. The uptake of these concepts in mainstream clinical practice has been slow, but perhaps is increasing as consensus statements, guidelines from rheumatological organization patients and internal reviews by third-party payors suggest that performing objective measurements and changing therapy accordingly are necessary to achieve optimal outcomes and to justify the use of medications, some of which are quite expensive. It will be interesting to see whether or not the treat-to-target strategy will ever be considered the standard of care in the USA, while in other countries this seems widely accepted already. The National Institute for Health and Clinical Excellence (NICE) clinical guidelines already stipulate that treat to target is the standard of care in the UK. It will also be interesting to see if different modalities and markers, such as those detected by current or new radiographic and laboratory technology, will be incorporated into future RA disease assessment paradigms and at what cost. Treat-to-target strategies may result in more aggressive treatments with more frequent use of combination drugs and biologics. Perhaps this will increase the cost of RA care even further, and rheumatologists may have to become stronger advocates as these costs are scrutinized ever more carefully by insurance companies and the government. Genomics and proteomics have the potential to change the practice of medicine dramatically, but whether or not these techniques and what they might really offer will ever be available in the rheumatology clinic remains to be established. Despite these questions, it appears that, in RA, the use of objective measures to guide treatment is a concept that is here to stay.

**Rheumatology key messages**

- Composite measures have been developed to define RA disease activity.
- Measurement of RA activity guides aggressive treatment to reach a predefined target.

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