Improving the Routine Management of Rheumatoid Arthritis: The Value of Tight Control

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ABSTRACT. Evidence is mounting that adopting a tight control approach to the management of patients with rheumatoid arthritis (RA) yields superior clinical outcomes including inhibition of progressive structural damage. While this approach has been successfully implemented in other chronic diseases, such as diabetes, its use in RA is less straightforward as there is not a simple “gold standard” measure for disease activity. A key component of the tight control approach is the availability of easily implemented and clinically relevant assessment measures of disease activity that allow physicians to monitor progress toward preset goals. This article summarizes the evidence from clinical trials demonstrating the benefits of achieving tight control and surveys the instruments available to assess patient progress in a consistent manner. A case study clearly demonstrates the benefits of the tight control approach in routine clinical practice. (First Release July 1 2010; J Rheumatol 2010;37:1570–8; doi:10.3899/jrheum.091064)

Key Indexing Terms:
DISEASE MANAGEMENT  BIOLOGIC THERAPY  PATIENT OUTCOMES  ASSESSMENT

Rheumatoid arthritis (RA) is a chronic and generally progressive systemic autoimmune disease that affects 0.5%–1% of adults worldwide, being more prevalent in women than in men, and in older people. RA is characterized by chronic inflammation of the synovial membrane of affected joints. Most patients also experience deterioration of cartilage and bone over time, leading to pain, disability, and premature mortality. Despite considerable therapeutic advances, many patients with RA experience active disease, progressive joint damage and disability, and comorbidities, including premature cardiovascular disease. No substantial improvement in survival rates has been observed over the last 40 years, although this situation may have begun to improve over the last decade, possibly due to changes in clinical practice and the availability of the newer biologic therapies. Among possible reasons for the relative lack of progress with regard to survival rates may be the infrequent use, in routine clinical practice, of suitable measures of disease control that can be used to set treatment goals and to monitor patients’ progress. While numerous research tools — such as the American College of Rheumatology (ACR) core data set and the Disease Activity Score (DAS) — are used in clinical trials, these complex instruments are unsuitable for busy rheumatology clinics. Consequently, treatment is generally determined on an individual patient basis without reference to appropriate targets, a process that has been likened to “giving treatment for a fever without a temperature, or rapid heart rate without a pulse”.

Recent improvements in the treatment of RA have meant that clinical remission is now a realistic target for many patients. Indeed, it is now widely accepted that setting remission as the goal of treatment is critical in order to prevent progressive joint damage. As a result of these developments, it is now essential that clinicians have an accurate, reliable definition of remission and are able to accurately measure low levels of disease activity.

The concept of “tight control” — treating patients to specified targets with aggressive therapy if necessary — has produced important benefits in conditions such as type I diabetes mellitus. For example, the Diabetes Control and Complications Trial showed that intensive treatment significantly reduced the risk of retinopathy progression and clinical neuropathy, and significantly lowered the risk of cardiovascular events versus standard treatment.

In routine clinical practice, achieving tight control has 2 prerequisites. First, a validated quantitative assessment is needed to facilitate continual monitoring of disease activity over time. Second, assessments need to be quick and easy to perform in routine clinical practice, and adaptable to multiple formats. Notably, tight-control studies in patients with diabetes or hypertension have shown that improved out-
comes can be achieved in well informed patients who understand the meaning of the parameters being investigated. This article examines recent clinical data demonstrating the potential benefits of tight control for patients with RA, and reviews some assessment tools that may be suitable for implementing tight control. Finally, a case study illustrating the difference tight control can make to individuals with RA is presented.

Advantages of Tight Control: Evidence from Clinical Trials

Several clinical trials have demonstrated the advantages of tight control in patients with RA. Among the first was the Finnish Rheumatoid Arthritis Combination Therapy trial, which compared disease-modifying antirheumatic drug (DMARD) combination therapy against DMARD monotherapy in patients with early RA. This study was one of the first to test whether the use of early aggressive combination DMARD therapy could alter the course of the disease by inducing long-lasting remission. Treatment aimed to achieve or maintain clinical remission, defined as meeting the criteria of no swollen joints, no tender joints, and no morning stiffness of > 30 minutes. Median disease duration was 5 weeks, with a range of 2-14 weeks. A substantial proportion of patients failed to achieve remission despite aggressive therapy, with only 28% of patients achieving remission (22% for monotherapy). Patients who failed to achieve remission were more likely to have psoriatic arthritis, persistent synovitis, and/or advanced radiographic damage.

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study compared an intensive management strategy with routine care in 111 patients with active RA\textsuperscript{17}. Intensively managed patients saw a rheumatologist every month and those who had not achieved a DAS $\geq 2.4$ received a dose increase or were switched to an alternative therapy. The study began in 1999, before the introduction of biologic therapies. All patients in the intensively managed group initially received SSZ, the dose of which was increased if DAS $\leq 2.4$ was not achieved. If responses remained insufficient, further treatment options included the addition of MTX, folic acid, and hydroxychloroquine. Patients in the routine care group saw a rheumatologist every 3 months and were treated at the physician's discretion. During this 18-month study, the mean improvement in DAS was significantly greater in the intensive management group than in the routine care group ($-3.5$ vs $-1.9$, respectively; $p < 0.0001$). Further, more patients in the intensive management group had a good response (decrease in DAS $\geq 1.2$, $82\%$ vs $44\%$; $p < 0.0001$) or were in remission (DAS $< 1.6$, $65\%$ vs $16\%$; $p < 0.0001$) than patients receiving routine care. Although conducted before the biologic therapies became a treatment option, the TICORA study clearly illustrates the principle that intensive management of patients using a predefined disease activity target is superior to management that does not involve a routine assessment of disease activity.

Results of the open-label CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) trial also support the contention that tight control is superior to conventional management in RA. In that study, intensive treatment with MTX was compared with conventional MTX treatment in patients with early RA\textsuperscript{18}. Patients in the intensive treatment group attended the outpatient clinic every month and their MTX dose was adjusted on the basis of predefined response criteria [swollen joint count, tender joint count, ESR, and visual analog scale (VAS) assessments of general well-being and pain] using a computerized decision program. Patients in the conventional treatment group attended clinic every 3 months and were treated according to standard practice. In the intensive treatment group, $50\%$ of patients achieved at least one period of remission during the 2-year trial compared with $37\%$ of those receiving conventional treatment ($p = 0.03$). Efficacy was significantly greater in the intensive group for almost all clinical variables, including morning stiffness ($p = 0.009$), ESR ($p = 0.007$), tender joint count ($p < 0.001$), swollen joint count ($p < 0.001$), VAS general well-being ($p < 0.001$), and VAS pain ($p = 0.001$).

Results of a recent study illustrate how intensive management of early RA can lead to very high rates of clinical remission\textsuperscript{19}. In this pilot study, 21 patients with early RA were treated with an intensified COBRA regimen (SSZ, MTX, and high-dose step-down prednisolone, intensified by adding hydroxychloroquine and continued low-dose prednisolone) with the option to further intensify MTX treatment after 8 or 21 weeks and to add infliximab therapy after 21 weeks\textsuperscript{19}. After 40 weeks of treatment, an impressive $19/21$ patients ($90\%$) had achieved remission (DAS28 $< 2.6$).

Other recent data suggest that tight control may improve long-term functional disability\textsuperscript{20} and reduce the need for joint surgery among patients with RA treated with an anti-tumor necrosis factor (TNF) agent\textsuperscript{21}. Tanaka and coworkers\textsuperscript{20} followed 2775 patients in an observational cohort study for whom 3 years of data were available. A significant correlation was found between tight disease control (DAS28 $< 2.6$) and functional disability score [using the Japanese version of the Health Assessment Questionnaire (HAQ)]; tight control was significantly associated with improving functional capability. A second study in patients receiving anti-TNF treatment for $\geq 1$ year found that mean DAS28 (including a measure of CRP levels) among patients who did not require joint surgery ($n = 70$) was significantly lower ($p < 0.001$) than among patients who required joint surgery ($n = 21$)\textsuperscript{21}. The authors concluded that tight disease control was important in reducing the need for joint surgery among patients receiving biologic therapy.

Together, the data discussed above support the hypothesis that tight disease control using a specified level of disease activity as a clinical target may improve outcomes for patients with RA. One caveat is that the majority of these studies assessed the use of nonbiologic therapies. The use of biologics is widespread in the treatment of RA, and is occurring earlier in the treatment process. Further studies would therefore be valuable to assess whether the same benefits are apparent if a tight control strategy is applied to treatment with biologics. Nonetheless, these results suggest that treating patients to specified targets improves clinical outcomes, regardless of the treatment. It may be that the specific treatment administered is less important than the principle of an intensive management strategy that includes regular monitoring of disease activity and adjustment of treatments as needed. In order to integrate a tight control approach into routine rheumatology practice, it is critical that there are suitable validated assessments of disease activity, and relevant and realistic clinical targets.

Assessments for Standard Clinical Care

Measuring disease activity and remission. Although recent advances in treatment have led to an increase in the proportion of patients reaching a state of remission\textsuperscript{22} there is no “gold standard” measurement of disease activity and remission in RA\textsuperscript{4}. Numerous pooled indices have been developed to measure disease activity, each of which incorporates 3–10 different assessments\textsuperscript{23,24,25,26,27,28,29,30,31}. This in turn means that several definitions of remission, all using different criteria, have been developed. No one disease activity index is consistently used, meaning that clinical trials throughout the world assess remission using different definitions. The ACR core data set\textsuperscript{25,27} and the DAS\textsuperscript{23,30,32} are
the most commonly used indices in clinical trials. The DAS assesses tender joint count, swollen joint count, ESR (or CRP, although this is less well validated than ESR\textsuperscript{24}), and the patient’s VAS estimate of general health; using a mathematical formula, the DAS score is calculated\textsuperscript{33}. The ACR core data set uses the same basic assessments as the DAS (tender joint count, swollen joint count, and measurement of ESR) plus physician’s and patient’s assessments of global disease activity and patient evaluations of pain and physical function\textsuperscript{25}. In addition, the ACR core data set measures change in disease activity, whereas the DAS measures current disease state or severity. The DAS is generally considered to have greater utility than the ACR core data set as it can be used to determine whether a patient has achieved low disease activity or remission. DAS28, a modification of the DAS involving only a simple joint count, has also been developed and is often used. Different definitions of remission in RA exist for each index; it is defined by DAS as a score < 1.6\textsuperscript{34}, by DAS28 as a score < 2.6\textsuperscript{23}, and by ACR as meeting a minimum of 5 ACR remission criteria for at least 2 consecutive months\textsuperscript{10}.

Another major set of DAS-based response criteria were developed by the European League Against Rheumatism (EULAR). These criteria combine an assessment of the change in disease activity from baseline with an analysis of the DAS reached at followup; patients are classed as having a good response, a moderate response, or no response\textsuperscript{34}. The main advantage of the HAQ is that it can be completed by the patient in 5–10 minutes. Its main limitations are a somewhat complex scoring calculation and the need to use a ruler to measure VAS scores\textsuperscript{4}.

To make the HAQ easier to use in standard rheumatology care, the multidimensional HAQ (MDHAQ) has been developed\textsuperscript{41}. The MDHAQ employs fewer questions than the HAQ; in addition, the VAS has been converted from a 10-cm line to 21 circles, making it easier to evaluate (Figure

<table>
<thead>
<tr>
<th>Elements</th>
<th>SDAI</th>
<th>CDAI</th>
<th>DAS</th>
<th>DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of swollen joints</td>
<td>Simple count (0–28)</td>
<td>Simple count (0–28)</td>
<td>More extensive joint counts (0–2.86)</td>
<td>Simple count, square root transformed (0–1.48)</td>
</tr>
<tr>
<td>No. of tender joints</td>
<td>Simple count (0–28)</td>
<td>Simple count (0–28)</td>
<td>Ritchie Index: graded joint counts; square root transformed (0–4.77)</td>
<td>Simple count, square root transformed (0–2.96)</td>
</tr>
<tr>
<td>Acute-phase reactants</td>
<td>CRP, mg/dl (0.1–10.0)</td>
<td>—</td>
<td>ESR, log transformed (0.23–1.51)**</td>
<td>ESR, log transformed (0.49–3.22)**</td>
</tr>
<tr>
<td>Patient global health</td>
<td>—</td>
<td>—</td>
<td>VAS, mm (0–0.72)**</td>
<td>VAS, mm (0–1.40)**</td>
</tr>
<tr>
<td>Patient global disease activity</td>
<td>VAS, cm (0–10.0)</td>
<td>VAS, cm (0–10.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Evaluator global disease activity</td>
<td>VAS, cm (0–10.0)</td>
<td>VAS, cm (0–10.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total index</td>
<td>No immediate scoring due to CRP; simple calculation possible (0.1–86.0)</td>
<td>Immediate scoring due to CRP; simple calculation possible (0.1–76.0)</td>
<td>No immediate scoring due to ESR; simple calculator required (0.23–9.87)</td>
<td>No immediate scoring due to ESR; simple calculator required (0.49–9.07)</td>
</tr>
</tbody>
</table>

* Based on transformation and weighting of individual elements according to the formula of the respective index; assumed ranges are 2–100 mm for ESR, and 0.1–10 mg/dl for CRP. Table reproduced with permission (Clin Exp Rheumatol 2005;23 Suppl 39:S100-8). ** The DAS and DAS28 formulae have also been modified to include CRP instead of ESR, and to substitute the patient global health by a constant. These versions are less commonly used and not well validated. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analog scale.
Table 2. Cutoff levels for disease activity states.36

<table>
<thead>
<tr>
<th>Scale</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>≤ 10</td>
<td>&gt; 10 and ≤ 22</td>
<td>&gt; 22</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>SDAI</td>
<td>≤ 11</td>
<td>&gt; 11 and ≤ 26</td>
<td>&gt; 26</td>
<td>&lt; 3.3</td>
</tr>
<tr>
<td>DAS28</td>
<td>≤ 3.2</td>
<td>&gt; 3.2 and ≤ 5.1</td>
<td>&gt; 5.1</td>
<td>&lt; 2.6</td>
</tr>
</tbody>
</table>

CDAI: Clinical Disease Activity Index; DAS28: 28-joint Disease Activity Score; SDAI: Simplified Disease Activity Index.

Figure 1. Comparison of visual scales used to assess pain. MDHAQ: Multidimensional Health Assessment Questionnaire. From Best Pract Res Clin Rheumatol 2007;21:755-87, with permission.
was reluctant to initiate biologic therapy. She decided to transfer her care as the rheumatologist on the definition used; further comparisons of disease portions of patients were found to be in remission depending on the definition used; several different definitions of remission are not always standardized. Several different definitions of remission are currently used, and so variation in remission rates between clinical trials may be due to the indices used, rather than the treatments received. Indeed, a recent study in which patients’ disease activity was assessed by different indices (including DAS28, SDAI, and CDAI) demonstrated that different proportions of patients were found to be in remission depending on the definition used; further comparisons of disease activity indices are therefore required. A collaborative committee between ACR and EULAR has been convened to develop a strict definition of remission that correlates with very low or no disease activity.

The case study below illustrates that routine disease assessment, using a simplified tool such as the CDAI, could provide valuable guidance when selecting initial therapy, and an indication of when treatment intensification or a switch in medication is required.

Case Study
A 42-year-old woman presented with a 12-month history of RA. Her primary care physician prescribed ibuprofen and prednisone, and referred her to a consultant rheumatologist. Her first rheumatologist initiated MTX 3 months after diagnosis and her symptoms initially improved before worsening. She decided to transfer her care as the rheumatologist was reluctant to initiate biologic therapy.

At presentation, her symptoms included morning stiffness (lasting 1 hour), polyarticular pain, fatigue, and difficulty with her work as a receptionist. The medication on presentation included MTX 20 mg/week, folic acid 1 mg/day, prednisone 5 mg/day, and ibuprofen 800 mg 3 times daily. Her baseline characteristics are shown in Table 3. Hand radiographs showed erosions at both second metacarpophalangeal (MCP) joints. With a CDAI of 23, she was considered to have high disease activity (Tables 2 and 3), while her SDAI and DAS28 indicated moderate disease activity (Tables 2 and 3). She was considered a suitable candidate for TNF inhibitor therapy and agreed to this course of treatment.

Following a negative tuberculosis skin test, etanercept 50 mg/week was initiated. The tight control model of optimal care was agreed upon, and treatment was temporarily increased to MTX 25 mg/week and prednisone 10 mg/day, while awaiting the full effect of etanercept therapy. CDAI was the principal assessment tool, with a treatment goal of low disease activity; SDAI and DAS28 were calculated when CRP levels were available.

Disease control during Years 1 and 2 are summarized in Table 3. After 1 month, the patient had low to moderate disease activity and the treatment regimen was continued. After 2 months, she was considered to have low disease activity and MTX was reduced to 20 mg/week and prednisone to 5 mg/day. After 3 months, disease activity scores were unchanged and the treatment regimen was maintained at this level. She continued to exhibit low disease activity over the following 2 years and prednisone was discontinued altogether after 6 months.

**Treatment modification on loss of disease control.** Two years after starting etanercept, she began to experience increased RA symptoms (Table 3) and fatigue. She had elevated liver function tests and radiographic evidence of one new erosion in her third left MCP joint. Prednisone was temporarily reintroduced at 20 mg/day, and tapered over 1 month. MTX was not increased because of the liver test abnormalities. At the 1-month followup visit, disease activity remained high, despite the higher prednisone dose.

Considering the next course of action, the results of the study by Finckh and coworkers were taken into account. That study suggests that on failure of a TNF inhibitor, switching to an agent with a different mechanism of action, such as B cell depletion, may be more effective in regaining disease control than an alternative TNF inhibitor. Therefore, rituximab was initiated (2 times 1000 mg infusions separated by 2 weeks), along with prednisone 10 mg/day and MTX 12.5 mg/week. One month later, the patient had low to moderate disease activity (Table 3) and at the 3-month followup visit, her CDAI was 8, indicating low disease activity. Liver tests had normalized and prednisone was decreased to 5 mg/day.

She continues to be seen in the clinic every 2 months. Her CDAI score remains low, suggesting good disease control, and her overall global and functional status remains good. Repeat hand radiographs 1 year after initiation of rituximab showed no new erosions. Based on recent data suggesting optimal disease control with fixed retreatment schedules and several trials suggesting 6-month intervals, she is receiving repeat courses of rituximab at this interval.
For this patient, TNF inhibition was initiated with the aim of achieving tight disease control. Low disease activity, measured using the CDAI, SDAI, and DAS28, was the clinical target. An increase in disease activity prompted reevaluation of treatment and a switch to an alternative biologic agent to regain tight disease control.

Conclusions
The concept of tight control — intensive disease management based on specific clinical variables — is well accepted in the management of many chronic conditions and has improved patient outcomes. In patients with RA, there is currently no gold standard for assessing disease activity and outcomes, so patients may not receive optimal treatment over time. Studies have shown that tight control and intensive treatment can significantly improve outcomes compared with standard approaches in RA, regardless of the treatment received. It remains to be seen whether tight control can not only control disease activity and reduce radiographic progression, but also reduce the increased risk of early cardiovascular morbidity and mortality due to inflammation-induced atherogenesis, an important comorbidity of RA. Nonetheless, the weight of evidence from well-designed controlled clinical trials indicates that the principles of tight disease control should now be applied by all physicians in routine clinical practice. The overriding principle of the tight control approach is not the choice of individual therapies but rather the regular monitoring of patients and early switching or adjustment of therapies that fail to adequately control disease activity. On a practical note, the implementation of tight control into routine care will require quick and simple validated tools for defining treatment targets and monitoring disease activity. Tools such as the CDAI and RAPID-3 appear to meet these requirements; in addition, the CDAI appears not only to provide simplicity but also, as recent studies suggest \cite{38, 39}, to be a more stringent tool for assessing remission. However, further studies are still needed to define the most appropriate assessment tools for assessing remission in routine clinical practice, as well as appropriate and achievable clinical targets reflecting tight disease control. Ultimately, the use of tight control should lead to treatment optimization and will provide the best chances of improvement and remission for patients with RA.

REFERENCES


