Developing an effective treatment algorithm for rheumatoid arthritis

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Abstract

RA is defined by the interrelated triad of disease activity, joint damage and disability. Although disease activity and its associated disability are reversible, joint damage and its associated disability are not. Thus, an important goal of RA therapy is to maximally reduce disease activity and thereby mitigate the accumulation of irreversible joint damage. Treatment for patients with RA should be initiated early and aggressively, with frequent assessments and a goal of achieving remission as quickly as possible after treatment initiation. We propose a treatment algorithm that recommends early and aggressive therapy with high-dose MTX therapy (15–25 mg/week), which may include moderate doses of glucocorticoids. The goal is to achieve low disease activity (determined by a composite measure that includes joint counts) within 3–6 months. If low disease activity is not achieved by 6 months, another conventional DMARD or a biologic agent should be added to the treatment regimen or patients should be switched to another DMARD plus a glucocorticoid. Once low disease activity is achieved, the treatment goal for the ensuing 3–6 months becomes disease remission.

Key words: biologic agents, clinical remission, rheumatoid arthritis treatment.

Introduction

RA is an autoimmune disease of unknown aetiology that primarily targets synovial tissues, cartilage and bone and is the most common form of immune-mediated arthritis [1, 2]. RA is defined by the interrelated triad of disease activity, joint damage and disability (Fig. 1). Disease activity represents the inflammatory disease process manifested by the pain, swelling and stiffness associated with RA; joint damage represents the destructive disease process; and disability represents the overall disease process characterized by reductions in both physical function and quality of life (QOL). Disease activity correlates with joint damage, as evidenced by the association between direct measures of inflammatory cytokine action (e.g. increased levels of CRP) [3] and radiographic progression [4, 5]. For example, in a study of patients with newly diagnosed RA, a highly significant correlation between CRP production and radiographic progression was observed during 3 years of follow-up ($P < 0.001$) [3]. Similarly, in a longitudinal study, fluctuations in disease activity (as assessed by the DAS) were associated with radiographic progression during a follow-up period of up to 9 years in patients with early RA [4]. Disease activity, as measured by the Simplified Disease Activity Index (SDAI), also has shown correlation with radiographic progression, as measured by total Sharp or Larsen scores [5, 6].

Conventional DMARDs (e.g. MTX), which have been for many decades and still are the mainstay of RA treatment, ameliorate clinical symptoms, reduce joint damage and allow a subset of patients to achieve remission [7]. The introduction of biologic agents—particularly biologic agent/conventional DMARD combinations—has resulted in further improvements in clinical outcome and greater effect on disease activity, functional capacity and structural damage [8]. Biologic agents include anti-TNF agents (infliximab, etanercept, adalimumab, certolizumab and golimumab), an anti-CD20 antibody (rituximab), a cytotoxic T-lymphocyte antigen-4 (CTLA-4), fusion protein (abatacept) and an anti-IL-6 receptor (IL-6R) agent (tocilizumab). Despite the availability of this wide array of new therapeutic options, treatment outcomes remain suboptimal. Approximately 50% of patients receiving anti-TNF agents do not achieve a substantial clinical response to therapy.

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Evidence indicates that to address the unmet need in RA treatment and to continue to improve outcomes, early intensive therapy is warranted and clinicians should strive to help their patients achieve remission even though it may not be a realizable goal for some. This review examines the case for early intensive RA treatment and presents suggestions for a treatment algorithm designed to achieve remission in a large proportion of patients.

The case for early RA treatment

Radiographic progression occurs early in the disease process, with a high proportion of patients experiencing joint damage in the first years of disease [12–14]. Further, there is evidence that the rate of radiographic progression may be greater during the first year than during the second and third years after diagnosis [15]. In one study, radiographic abnormalities were observed in 39 (93%) of 42 patients, with a disease duration of <2 years [16]. Notably, structural damage also may occur before it is visible on a radiograph [12]. In a study of patients with early RA, MRI at 4 months after symptom onset identified carpal erosions in 45% of patients, but 15% had erosions on plain radiographs [12].

Long-term radiographic evidence from the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) highlights the importance of combination therapy early in disease progression. TEMPO was a double-blind study evaluating the efficacy of MTX monotherapy compared with MTX plus etanercept in patients who were unresponsive to at least one DMARD other than MTX [17]. At 3 years, data from the TEMPO trial demonstrated that although aggressive therapy with a current treatment may stop joint destruction, it will not reverse the accumulated damage [18]. Although disease activity-related disability, characterized by inflammation-induced joint tenderness, pain, and stiffness, leads to disability that is reversible, the disability associated with joint damage is irreversible [19]. These different forms of disability are not distinguishable, as measured in the HAQ Disability Index (HAQ-DI). However, two separate categories were developed to distinguish disease activity-related disability (ACT-HAQ), which reflects functional limitations from current RA activity, from damage-related disability (DAM-HAQ), which reflects damage that is irreversible (i.e. not responsive to RA treatment with DMARDs) [20]. Of note, the irreversible component of disability progressively increases with increased duration of disease. For patients with early disease, the total HAQ score is primarily attributed to the ACT-HAQ, whereas the DAM-HAQ accounts for a lesser amount of the total HAQ score. However, as the disease progresses, the DAM-HAQ becomes an increasingly greater component of the HAQ score [20]. This suggests that the structural damage associated with continued disease activity raises the baseline (floor) of disability, making it increasingly difficult for functionality to be normalized [21].

In addition to occurring early in the course of the disease and during states of moderate and high disease activity, structural damage can occur among patients with a low state of disease activity. In an analysis of data from the Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE), joint damage was demonstrated to increase with increasing levels of disease activity [5]. However, even in patients taking MTX who achieved low disease activity by week 14, radiographic progression was seen by week 54 [5].

Higher radiographic scores remain associated with a higher level of irreversible functional limitation regardless of whether patients ultimately achieve remission (and, hence, in whom disease activity and the associated reversible component of disability are minimized) [19]. In an analysis of data from six clinical trials, the reversibility of HAQ scores decreased with increased duration of RA and with higher radiographic scores [19]. Therefore, irreversible functional impairment leads to a reduction in the sensitivity to change in HAQ scores [22]. Consequently, the functional benefits that can be achieved when patients are treated early in the course of the disease may not be achievable in patients with late RA. Overall, these findings underscore the importance of attaining disease remission early in the course of the disease.

The case for intensive RA treatment: treating to a target

Internationally developed recommendations suggest frequent measurement of disease activity to facilitate achievement of remission in the fastest possible manner [23, 24]. These recommendations are based on data suggesting that early and aggressive therapy is associated with improved clinical outcomes. The Tight Control for Rheumatoid Arthritis (TICORA) study demonstrated that tight control and clinical measurement of disease were associated with disease remission and a decreased risk of radiographic progression [25]. In this single-blind study,
patients were randomly assigned to routine outpatient care (control) or intensive outpatient care with conventional DMARDs and were followed up for 18 months. The routine care group was seen every 3 months; no formal composite disease activity measure was used to guide clinical decisions. Intensive care consisted of monthly outpatient assessments—objective assessment of disease activity, IA CS injections and the targeting of persistent disease activity using a protocol to escalate DMARD therapy. At 18 months, patients in the intensive care group had achieved significantly higher ACR 20/50/70 responses (91%/84%/71%) than had the routine care group (64%/40%/18%; \( P < 0.0001 \) for all comparisons) [25]. The percentages of patients reaching good European League Against Rheumatism (EULAR) response (i.e. DAS <2.4, 82 vs 44%; \( P < 0.0001 \)) and remission (DAS <1.6, 65 vs 16%; \( P < 0.0001 \)) were also significantly higher in the intensive care group. Further, radiographic progression, as assessed by total Sharp scores and erosion scores, was significantly reduced in the intensive care group compared with the routine care group [25].

The Dutch Behandel Strategieen (BeSt) study extends the results of TICORA on the value of aggressive therapy with biologic agents [26, 27]. In this study, patients with early RA were randomly assigned to one of four different treatment strategies: (i) sequential monotherapy; (ii) step-up combination therapy; (iii) initial combination therapy with tapered high-dose prednisone; or (iv) initial combination therapy with infliximab. Initial combination therapy, including either prednisone or infliximab, was associated with significantly greater functional improvement at 3 months compared with sequential monotherapy and step-up combination therapy [26]. At 3 months, disability, as measured by the Dutch version of the HAQ (D-HAQ), was significantly lower in the initial combination therapy groups (0.6 for both) compared with the sequential monotherapy and step-up combination therapy groups (1.0 for both; \( P < 0.05 \) for groups 1 and 2 vs groups 3 and 4) [26]. At 12 months, differences between the initial combination therapy groups and the sequential monotherapy group remained significant. Radiographic progression also was significantly lower in the initial combination therapy groups [26]. After 2 years, groups 3 and 4 experienced significantly less radiographic progression than groups 1 and 2, as assessed by median changes from baseline in Sharp/van der Heijde scores [27]. These results highlight the cost of treatment delay and support the use of early intensive treatment to suppress disease activity so that joint damage and disability are minimized.

**Developing an appropriate treatment algorithm**

When designing an individual treatment regimen, it is important to keep the RA triad (i.e. disease activity, joint damage and disability) in mind. Current goals for the treatment of RA include relief of symptoms (e.g. fatigue, pain, swelling and stiffness); prevention of joint destruction, loss of joint function, deformity and disability; preservation of QOL; and achievement of remission. However, it is important to also note that remission may not be possible in patients with late-stage disease. Therefore, the goal of therapy in these patients is to decrease disease activity as much as possible. To achieve this, it has become increasingly clear that even maintaining a state of low disease activity is insufficient. Even though good results were seen with aggressive intervention in TICORA and BeSt, the low disease activity target for these studies allowed radiographic progression to continue [25-27]. Given that progressive joint damage can occur and functional impairment exists even during low disease activity, it is important to attempt to bring the patient’s disease to the lowest degree of disease activity possible, which is usually remission. Thus remission, defined as a state with no evidence of significantly active disease [i.e. no swollen and painful joints and no acute-phase response [28] or \( \leq 1 \) tender joint count (TJC), swollen joint count (SJC), CRP \( \leq 1 \) mg/dl, and patient global assessment \( \leq 1 \) cm, or SDAI \( \leq 3.3 \) or Clinical Disease Activity Index (CDAI) \( \leq 2.8 \) [28], should be the target of therapy [28, 29]. Early sustained remission has been shown to prevent the progression of joint damage, whether the treatment consists of conventional DMARDs or biologic agents [5]. While remission remains the desired outcome, the risks and benefits of more intensive therapy must be evaluated for each patient.

Predictors of response can be useful to enable patients to proceed to the lowest possible level of disease activity as rapidly as possible. An evaluation of large clinical trials examining the efficacy of MTX monotherapy or MTX/anti-TNF combination therapies found that disease activity levels achieved at 3 months were highly predictive of remission at 1 year [30]. Patients with high levels of disease activity at 3 months were unlikely to achieve low levels of disease activity at 1 year (Fig. 2) [30]. Therefore the ability to predict treatment response early in the course of therapy furthers the goal of achieving rapid control of disease activity while minimizing exposure to ineffective, but costly and potentially toxic, therapies. Commonly used instruments for assessing treatment response in clinical trials of RA are the ACR response criteria and DAS scores. However, logistic constraints are associated with the use of the ACR response criteria in practice because they do not allow assessment of the disease activity level or state [31].

The CDAI is a simplified assessment scale that is sensitive to changes in disease activity, performs more complex indices [e.g. DAS/DAS-28 (28-joint DAS) and ACR improvement criteria] and is easier to calculate and use in clinical practice [8, 31]. Importantly, the CDAI does not require laboratory measurement of acute-phase reactants, allowing for more immediate therapeutic decisions [32]. Moreover, patients achieving a low disease state according to the CDAI measure are less likely to show radiographic evidence of disease progression [6]. As such, CDAI may be a better target than DAS-28.

An initial treatment algorithm that incorporates the goal of achieving rapid disease remission is illustrated in
This proposed algorithm was derived from recommendations based on evidence from five literature reviews performed for synthetic DMARDs, biologic DMARDs and glucocorticoid treatment strategies. The literature reviews were discussed and summarized as an expert opinion in the course of a Delphi-like process. The algorithm recommends early initial and intensive therapy with high-dose MTX therapy, which may include moderate doses of glucocorticoids [34]. The goal is to achieve low disease activity (determined by a composite measure that includes joint counts such as DAS-28, SDAI and CDAI; Table 1 [32]) within 3–6 months. For patients who do not exhibit any improvement by 3 months, treatment should be adjusted immediately; for those who exhibit improvement within this time frame but do not achieve DAS, SDAI or CDAI low disease activity, an additional 3 months of observation is warranted. If low disease activity or remission is not achieved by 6 months, another conventional DMARD or biologic agent should be added to the treatment regimen or patients should be switched to another DMARD plus a glucocorticoid. Several published studies favour the addition of a biologic agent in MTX inadequate responders over the use of SSZ in addition to MTX [35, 36].
### Discussion

The elements of the RA triad (i.e., disease activity, joint damage and disability) are important to keep in mind when approaching RA therapy. It is now well established that disease activity leads to both joint damage and disability. However, although the disability related to disease activity is reversible, joint damage remains irreversible and leads to irreversible disability. Thus the focus of therapeutic attention should be the maximum possible reduction of disease activity as soon as possible because this will halt the accrual of joint damage and lead to maximum reversal of disability. Disease remission, however, is the ultimate goal because even low disease activity may be associated with joint damage and functional impairment. To prevent the accumulation of irreversible damage, treatment should be initiated early and aggressively and assessments should be performed frequently, with a goal of achieving remission as quickly as possible after treatment initiation.

Recent guidelines and criteria put forth by ACR and EULAR have updated the current definition of clinical remission [29]. The joint committee suggested that clinical remission be defined by the fulfillment of either of these definitions: (i) when scores of TJC, SJC, CRP (milligram/deciliter) and patient global assessment score are ≤1; or (ii) when the SDAI score is ≤3.3. The hope is that this treat-to-target approach may result in better outcomes than does the approach currently used, and that the revised definition of clinical remission may serve as the appropriate target for many patients [29].

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**Table 1** Composite measures of disease activity (elements of composite indices and their potential contributions to the total index) [32]

<table>
<thead>
<tr>
<th>Element</th>
<th>SDAI</th>
<th>CDAI</th>
<th>DAS</th>
<th>DAS-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of swollen joints</td>
<td>Simple count (0/C150</td>
<td>Simple count (0/C150</td>
<td>Simple count; square root transformed (0/1.48)</td>
<td></td>
</tr>
<tr>
<td>No. of tender joints</td>
<td>Simple count (0/C150</td>
<td>Simple count (0/C150</td>
<td>Simple count; square root transformed (0/1.48)</td>
<td></td>
</tr>
<tr>
<td>Acute-phase reactants</td>
<td>CRP, log transformed (0.49/3.22)</td>
<td>ESR, log transformed (0.23/4.77)</td>
<td>ESR, log transformed (0.49/3.22)</td>
<td>ESR, log transformed (0.49/3.22)</td>
</tr>
<tr>
<td>Patient global disease activity</td>
<td>CRP in milligrams/deciliter (0.1/10.0)</td>
<td>ESR in millimeters (10.0)</td>
<td>Patient global disease activity</td>
<td>ESR in millimeters (10.0)</td>
</tr>
<tr>
<td>Patient global health</td>
<td>VAS in millimetres (0.0/100)</td>
<td>VAS in millimetres (10.0)</td>
<td>Total index</td>
<td>VAS in millimetres (10.0)</td>
</tr>
</tbody>
</table>

*Based on the transformation and weighting of individual elements according to the formula of the respective index (assumed ranges are 2–100 mm/h for ESR and 0.1–10 mg/dl for CRP). The DAS and DAS-28 formulae have also been modified to include CRP instead of ESR and to substitute the patient global health by a constant VAS: visual analogue scale.

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**Rheumatology key messages**

- RA-induced joint damage and its associated disability are not reversible.
- The goal of RA therapy is to reduce disease activity and mitigate the accumulation of irreversible joint damage.
- RA treatment should be initiated early and aggressively, with the goal of achieving remission.
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References


Algorithm to treat RA


