

Initial Management of Rheumatoid Arthritis

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KEYWORDS

- Rheumatoid arthritis • Disease-modifying antirheumatic drug
- DMARD

Key Points

- Half of patients who have rheumatoid arthritis (RA) which is diagnosed and treated early by a rheumatologist with the goal of remission or low disease activity can expect to achieve remission while taking their disease-modifying antirheumatic drugs.
- Recently, the recognized benefits of very early therapy of RA highlighted the need to make the diagnosis of RA as early as possible.
- Therapeutic goals and the ability to measure them are critically important in treating any disease.

The prognosis for the patient with newly diagnosed rheumatoid arthritis (RA) has dramatically changed over the last two decades. If a patient is diagnosed and treated early by a rheumatologist with the goal of remission or low disease activity, half of patients can expect to achieve remission while taking their disease-modifying antirheumatic drugs (DMARDs). Strong evidence exists that early diagnosis and aggressive treatment alter the natural history of RA. Clearly, prevention of permanent structural damage to joints, including both erosions and joint-space narrowing as measured on radiographs, but also the prevention of deformities that can occur without erosions, is a strong rationale for early RA treatment.^{1,2} Structural damage, when it reaches a critical level, is associated with functional impairment. Although there is evidence in some cases that erosions may heal (at least radiographically), joint-space narrowing and subluxations are permanent.³⁻⁶ A meta-analysis of 12 studies demonstrated significant reduction of radiographic progression in subjects treated early when compared with the subjects treated later. An average delay of 9 months in starting DMARDs significantly

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increased radiographic progression. Subjects with more aggressive erosive disease benefited the most from early therapy.⁷ However, it is important to note that most patients who have RA fall into the category of poor prognosis by virtue of erosions at baseline, or rheumatoid factor (RF) or cyclic citrullinated peptide (CCP) positivity, and clearly need early intervention.

Some investigators have suggested that there is a window of opportunity in early disease during which therapy is somehow particularly effective. Much data, some referenced above, clearly show that the earlier physicians treat, the better patients do. Most large trials in early disease show a strong correlation of disease duration to outcomes.^{8–10} No one can argue that earlier is better, but the window of opportunity concept can be, and sometimes is, carried too far. It should not be assumed that this window somehow closes and then patients do not benefit from therapy. Excellent data demonstrate that in the face of active disease, patients benefit from appropriate DMARD treatment regardless of disease duration.^{11–17} It remains debatable whether early therapy can reset the radiographic progression rate of patients for years to come. The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) and the Combination Therapy in Patients with Early Rheumatoid Arthritis (COBRA) trials (see later discussion), among others, suggest this may be true. It is important to keep in mind the many limitations of the open long-term observational nature of these results and how aggressively subjects from these trials were treated to target.

Long-term results (5-year and 11-year) of the FIN-RACo trial suggest that effect of early aggressive intervention on radiologic progression is longlasting.^{18–20} In this study, subjects were randomized into two groups. From the start, one group received a combination of DMARDs, including methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ), and the other group received SSZ as monotherapy. The first group had prednisolone as part of their regimen; in the second group it was used as needed. After the initial 2 years, the drug regimen became unrestricted and, therefore, similar. At 5 and 11 years, radiologic progression in the SSZ-alone group was significantly higher than in the group treated with the combination of DMARDs. Similar results were demonstrated in the COBRA trial.^{21–23} In this trial, 155 subjects were randomized to COBRA therapy (SSZ 2 g/day, MTX 7.5 mg/week, prednisolone starting at 60 mg/day and tapered to 7.5 mg by the seventh week) or SSZ (2 g/day) monotherapy. At 28 weeks, prednisolone was tapered and withdrawn and, after 40 weeks, MTX was stopped. After this, treatment in both groups became unrestricted. Analysis at 5 and 11 years showed a significantly higher rate of radiologic progression in the SSZ group. Both the COBRA and FIN-RACo studies support the hypothesis that aggressive therapy in the early phase of RA results in long-term radiologic benefit that may translate into better functional outcome.

How soon is soon enough? There really is no answer to this question. Treatment within the first 3 months of onset is a goal. A study of a cohort of subjects with early RA with disease duration less than 12 months, treated with tight-control protocol, showed that a major predictor of an American College of Rheumatology (ACR) clinical remission at 12 months is the duration of disease at the time of initiation of treatment. Very early RA was defined as disease with symptoms of less than 12 weeks. Multivariate analysis demonstrated that the only independent predictor of erosives at 12 months was an increase in duration of disease at the time of initiation of treatment (odds ratio [OR] 2.4; CI 1.1–5.6).²⁴

EARLY DIAGNOSIS (CLASSIFICATION) OF RA

Recently, the recognized benefits of very early therapy of RA highlighted the need to make the diagnosis of RA as early as possible. With this goal in mind, the ACR and

European League Against Rheumatism (EULAR) collaborated on a new set of criteria that were meant to distinguish inflammatory arthritis (arthritis that needed MTX treatment) from noninflammatory arthritis. The results were the ACR-EULAR 2010 Classification Criteria (**Table 1**).²⁵ The 1987 ACR classification criteria for RA remain very useful for discriminating inflammatory from noninflammatory arthritis. However, because 6 weeks of symptoms are required and they do not include anti-CCP positivity, the 1987 criteria are not as useful in early disease.^{26,27} The goal of the new criteria was to provide a uniform approach to identify individuals with undifferentiated synovitis who have the highest probability of developing persistent RA and structural damage and, therefore, individuals who would benefit from early DMARD intervention. The new classification criteria will also allow more uniform disease definition and subject recruitment into clinical and epidemiologic studies in early RA.

Importantly, compared with the 1987 criteria, 6 weeks of symptoms is not required and anti-CCP antibody positivity is included. In the new criteria, 6 weeks or more of symptoms are not required, but they do give an extra point and increase the specificity for ongoing disease. Analysis of 2010 RA criteria performance by Cader and colleagues²⁸ demonstrated, not surprisingly, that 2010 criteria identify more subjects with RA earlier than 1987 criteria (42% vs 23%, respectively; $P < .0001$). However, more subjects whose arthritis resolved spontaneously were classified initially as definite RA

A. Joint involvement	0–5
1 large joint ^a	0
2–10 large joints	1
1–3 small joints ^b (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	0–3
Negative ^c RF and negative ACPA	0
Low-positive ^d RF or low-positive ACPA	2
High-positive ^e RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	0–1
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	0–1
<6 wk	0
≥6 wk	1

When RF information is available only as positive or negative, a positive result should be scored as low-positive.

Abbreviations: ACPA, anticitrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

^a Shoulders, elbows, hips, knees, ankles.

^b Metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

^c Values less than or equal to the upper limit of normal for the laboratory and assay.

^d Values higher than the upper limit of normal but three or less times the upper limit of normal.

^e Values more than three times the upper limit of normal for the laboratory and assay.

Adapted from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62(9):2569–81.

by 2010 criteria than 1987 criteria (8% vs 2%, respectively; $P = .01$). After 18 months, both criteria performed the same in identifying subjects with RA. A retrospective study by Kaneko and colleagues²⁹ showed that 2010 criteria have better sensitivity in identifying RA than 1987 criteria (73.5% vs 47.1%, respectively), but less specificity (71.4% vs 92.9%, respectively). Conversely, in the subgroup of subjects who are negative for RF and anti-CCP antibody, the 2010 criteria have a sensitivity of only 15.8%. Although useful to identify disease early, clinicians have to be mindful of potential limitations of 2010 criteria: lower specificity than the old criteria and potentially low sensitivity in seronegative RA.

ANTI-CCP IN EARLY DIAGNOSIS OF RA

Many studies have shown that autoantibodies are seen in people who have no symptoms or physical findings of arthritis but who will develop RA years later.^{30–37} Anti-CCP antibodies seem to be the most important of these. Anti-CCP has been shown to be reasonably sensitive (65%–80%) and highly specific for RA (98%).^{38–43} Importantly, a study by van Gaalen and colleagues⁴⁴ demonstrated that presence of anti-CCP antibodies predicts progression of undifferentiated arthritis to RA independently of other factors. For 3 years, 318 subjects with undifferentiated arthritis (**Table 2**) were followed. After 3 years, 93% of the subjects who were CCP-positive developed RA by the 1987 criteria (99% by 2010 criteria) compared with only 25% of the subjects who were CCP-negative. This demonstrates the usefulness of this test in patients with undifferentiated inflammatory arthritis. Because of the inclusion of CCP positivity in the 2010 criteria, many of the subjects in the above study would have been classified as RA at baseline.

THE NEXT STEP? THE CONCEPT OF PRECLINICAL RA

As mentioned above, people who later develop RA frequently have CCP and RF antibodies present in their serum for years before they develop clinical RA. This takes the discussion of early treatment to a whole new level and leads to speculation about the possibility of treating or modifying risk factors in these people to prevent the onset of clinical disease.^{45–49} Obviously, this raises several questions, not the least of which are how to identify these people in the first place and what risks of therapy are acceptable in people who do not yet have clinical disease? RA has a prevalence of less than 1%. Therefore, CCP used in the general population is not a good screening test, even with sensitivity between 96% and 98%. Far more false positives would be identified than true positives if used in the general population. Despite all these issues,

Table 2
Anti-CCP antibodies and prediction of RA in patients with undifferentiated arthritis

	Patients Fulfilling ACR RA Criteria, Number (%)		
	After 1 y	After 2 y	After 3 y
Anti-CCP-positive (n = 69)	57 (83)	62 (90)	64 (93)
Anti-CCP-negative (n = 249)	46 (18)	60 (24)	63 (25)

Multivariate analysis showed that anti-CCP positivity in undifferentiated arthritis is the most important predictor of future diagnosis of RA (OR = 38.6, CI 9.9–151.0).

Adapted from van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004;50(3):709–15.

preventive trials are in the planning stages for people at high risk for the future development of RA.

Goals for Early RA Treatment

Therapeutic goals and the ability to measure them are critically important in treating any disease. This is certainly true in RA treatment and, until recently, clear goals have been elusive. Rheumatologists have long envied the endocrinologists with their hemoglobin (Hgb) A1C or the cardiologists with their blood pressure measurements and low-density lipoprotein levels. Recently, the rheumatologic world has embraced the concept of having a goal or target for therapy in RA as important, and the ACR has endorsed several different measures of disease activity in RA. These include the Disease Activity Score (DAS) 28, the Clinical Disease Activity Index (CDAI), the Simplified Disease Activity Index (SDAI), the Routine Assessment of Patient Index Data, and the Patient Activity Scale.^{50–57} Although it may seem intuitively obvious that having a target and treating to this would be beneficial, the Tight Control for Rheumatoid Arthritis (TICORA) study showed this for the first time. In TICORA, subjects were randomly assigned to intensive management or routine care. Escalation of therapy in the intensive group was based on monthly measured DAS. If the DAS was greater than 2.4, therapy was escalated. Escalation of therapy in the routine group was done at the discretion of the rheumatologist without particular disease activity index recordings. At 18 months, subjects in intensive therapy were doing better in all respects—clinically and radiographically.⁵⁸

Rheumatoid arthritis treatment guidelines from the ACR and EULAR recommend monitoring disease activity and treating it to a target of at least low disease activity.^{59–61} Remission is the ultimate goal of treatment, but it is unclear whether this should be the target for all patients. If a patient is on MTX alone (or any other therapy), is very close to remission, is happy, and has no problems with activities of daily living, does it make sense to add a biologic to their program? This is when the art of medicine still plays an important role. As these decisions are made, efficacy, toxicity, and the cost of adding and not adding additional therapy must be carefully weighed. The endocrinologists have taught that lower is not always better; aggressive HgbA1C lowering trials pushed too far result in unacceptable toxicities.⁶²

Recognition of remission in RA has been difficult because of the many different definitions used.^{63–69} Fortunately, there is now one uniform definition, at least for clinical trials: the new ACR-EULAR remission guidelines. It was proposed that, in the setting of clinical trials, a subject is in remission when scores of swollen-joint count, tender-joint count, patient global assessment, and CRP are all less than or equal to 1 or when the score on the (SDAI) is less than or equal to 3.3. Importantly, analysis by Felson and colleagues⁷⁰ showed that DAS 28 at cutpoint less than 2.6 or less than 2.0 did not ensure good radiologic outcomes. The new ACR-EULAR proposed definition is still waiting for further validation.⁷¹ What the remission definition for clinical practice should be remains an important question. One set of criteria might not be suitable for heterogeneous groups of patients who are not in a trial setting. CDAI less than or equal to 2.8 and a cumulative score of less than or equal to 1 for swollen-joint count, tender-joint count, and patient global assessment seem to have good predictive validity for remission in the clinical setting.^{72–74}

An international task force developed treat-to-target recommendations to achieve optimal therapeutic outcomes in RA.⁷⁵ This task force had the following suggestions or recommendations:

- Sustained clinical remission is the primary target in treating RA.

- In some circumstances, when a state of complete remission is not possible (eg, significant joint damage, failure of multiple treatment regimens, toxicities, or cost issues), low disease activity could be an acceptable alternative target.
- A patient's disease activity should be followed every 1 to 3 months until the target is reached, with subsequent assessments every 3 to 6 months.
- Validated composite disease activity indices should be used in routine clinical practice.

The Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study demonstrated that adapting treat-to-target strategy aiming at remission in the setting of clinical practice is realistic.⁷⁶ Because this trial was done before the new remission definition was available, several definitions were evaluated. Full ACR, modified-ACR criteria, DAS 28 with different cutoffs, SDAI less than 3.3, and CDAI less than 2.8 were used to define remission in this trial.

INITIAL THERAPY IN EARLY RA: MONOTHERAPY OR COMBINATION, BIOLOGIC OR NONBIOLOGIC

Despite tremendous advances in RA treatment, many questions remain about initial therapy, and the art of medicine is again important. Many studies have shown that combination of DMARDs is more effective than monotherapy.^{19,22,77–88} Four potential approaches in combining DMARDs are (1) parallel administration of DMARDs (eg, MTX, SSZ, and HCQ combinations; triple therapy) from the start, (2) the step-up approach (addition of second and, potentially, third DMARD in patients with initial inadequate response), (3) the step-down approach (initial administration of combination therapy with subsequent withdrawal of drugs if good control of disease is achieved), and (4) initial combination of nonbiologic and biologic DMARDs. Goekoop-Ruiterman and colleagues^{77,78} examined four different initial treatment approaches in RA. In the Behandel-Strategieën (BeSt) study, subjects were randomly assigned to (1) methotrexate monotherapy, (2) step-up combination to three DMARDs (triple therapy), (3) combination of MTX, SSZ, and high dose prednisone, or (4) combination of MTX with infliximab. Therapy in all groups was adjusted every 3 months if the DAS was greater than or equal to 2.4. If the DAS was less than 2.4 for more than 6 months, medications were withdrawn until one drug remained for maintenance. Groups 3 and 4 (the initial combination groups) had more rapid clinical improvement during the first year and less progression of radiographic joint damage. However, after 2 years, similar clinical and functional improvement was noted across all four groups even though, by that time, subjects in all groups were on many different therapies. This study highlights two very important points:

1. Therapy should be individualized for each patient.
2. Treating to a target as per the TICORA trial is the critical factor to achieve outcomes regardless of the therapy used.

With the results of the BeSt trial, some rheumatologists have advocated combinations up front for all patients, based on the radiographic benefit; others have advocated the step-up approach because clinical outcomes of all groups in the BeSt trial were indistinguishable at 2 years. The Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial addressed this question in early (mean duration 3.6 months), poor prognosis (all subjects who were RF-positive, CCP-positive, or had at least two erosions) RA.⁸⁹ This trial was the largest (755 subjects) investigator-initiated, double-blind, randomized trial ever in early RA. Half of the subjects were randomized to receive combinations up

front (either MTX and etanercept or MTX, SSZ, and HCQ [triple]) while the other half received MTX alone (20 mg/week). At 6 months, subjects who took the MTX alone stepped up to combinations if the DAS28 score was greater than 3.2 (step-up occurred for 72% of subjects). The primary outcome was the mean DAS28 for subjects between weeks 48 and 102. No difference was seen between step-up and initial-combination subjects (mean DAS28 3.2 vs 3.2, respectively; $P = .75$). There was also no difference for radiographic progression. In this trial, 28% of subjects started on MTX had a great response (DAS28 <3.2) and did not need additional therapy. This number is very similar to that found in the BeSt trial and Swedish Farmacotherapy trial (SWEFOT). Thirty percent of subjects with early RA did well on MTX monotherapy.^{90,91} Importantly, TEAR teaches that those patients who do need a step-up do well and have clinical and radiographic outcomes identical to those of the patients who received combinations up front. Therefore, it seems prudent to initiate therapy with MTX and then, at 3 to 6 months, step up to combinations only with patients that still have DAS28 greater than 3.2. With regard to which combination to step up to, in the TEAR trial there was no advantage of etanercept over SSZ- HCQ; therefore, it would seem prudent to use the far less expensive SSA-HCQ first.^{92,93}

HEALTH CARE MAINTENANCE IN EARLY RA

When faced with a patient with recent onset RA, rheumatologists have rightly focused on getting the disease under control as rapidly as possible. However, with the excellent outcomes of most patients, attention should also be directed to important health-care maintenance issues. In particular, concern should be on cardiovascular risk factors, immunization status, and bone health. With the well-known excess morbidity and mortality in this patient population attributable to cardiovascular disease, risk factors such as obesity, hypertension, sedentary lifestyle, and lipids should be addressed by the rheumatologist or addressed in a close partnership with the primary care physician.^{94–96} If statins are necessary, they have the added benefit of decreasing the DAS of the RA.^{97–99} All patients with RA should be up-to-date on all immunizations. It is prudent to think about this early in the course of disease because many of the DMARDs, including MTX, will blunt the response to immunization.^{100–103} Therefore, if at all possible, all appropriate patients should receive their pneumococcal vaccination before MTX therapy. Further, all indicated live vaccines (usually zoster vaccine) should be given at least 2 weeks before biologicals. Therefore, it is better to do it in the very beginning than to have to delay biologic therapy later.¹⁰⁴ Finally, especially in postmenopausal women, bone density status should be known and appropriate treatment, usually bisphosphonate, prescribed.¹⁰⁵ Unless contraindicated, all patients with RA should be on adequate calcium and vitamin D. Although lung cancers and lymphomas are overrepresented in patients with RA, other health-care maintenance should be appropriate for the patient's age.

UNANSWERED QUESTIONS: THE WAY FORWARD

Currently there are at least three major questions that, when answered, will allow major steps forward:

1. How can we predictably select the best therapy for each individual patient?
2. Would patients benefit from induction approaches in RA and, if so, which patients?
3. What should the goal or target be in RA, and is the current definition of remission adequate for this?

The next major advance in treatment in early RA will occur when differential selection can identify which patients will benefit most from which therapies and, perhaps, which patients are at risk for toxicities from the therapies. Who are those 30% of patients that need only MTX initially? Which patients need triple therapy up front? Which patients need a biologic from the onset and which biologic? Which patients might have great responses to HCQ or SSZ monotherapy? To address these questions, clinical trials are needed designed to answer these questions and, importantly, biomarkers are needed that are linked to well-defined clinical outcomes, preferably from randomized clinical trials.

Recently, the ACR published the results of a workshop on RA clinical trial issues.¹⁰⁶ This group of experts highlighted these priorities and highlighted the need for biomarkers to be included in all trials. The trials needed to address these questions will, for the most part, not come from the pharmaceutical industry because most of the questions will require comparison of different medications and approaches, and not necessarily new products. It is unclear where funding for these needed trials and biomarker collection will come from, but partnerships between all interested parties are a must. Recently, health care systems, such as the Department of Veterans Affairs, have stepped up and funded important trials that will ultimately make treatment of RA, not only better, but more economical. Although new medications are always welcome, if current medications were used to the best advantage, it would be a huge leap forward for patients with RA.

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