My Treatment Approach to Rheumatoid Arthritis

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Abstract

The past decade has brought important advances in the understanding of rheumatoid arthritis and its management and treatment. New classification criteria for rheumatoid arthritis, better definitions of treatment outcome and remission, and the introduction of biologic response-modifying drugs designed to inhibit the inflammatory process have greatly altered the approach to managing this disease. More aggressive management of rheumatoid arthritis early after diagnosis and throughout the course of the disease has resulted in improvement in patient functioning and quality of life, reduction in comorbid conditions, and enhanced survival.

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Rheumatoid arthritis is the most common autoimmune disease that affects the joints. Worldwide, approximately 1% of the population is affected, with higher prevalence in persons of European or Asian ancestry.[1] Rheumatoid arthritis can develop in persons of any age, with the typical age at onset of about 55 years. The prevalence of rheumatoid arthritis increases considerably with age, affecting approximately 6% of the white population older than 65 years. In the United States, the lifetime risk of developing rheumatoid arthritis is 3.6% in women and 1.7% in men. There is some indication that the risk of developing rheumatoid arthritis has increased somewhat in recent years, at least in women.[2]

Clinical features of rheumatoid arthritis typically include symmetric polyarthritis with joint swelling, especially of the hands and feet, although any of the appendicular joints may become involved. Patients with rheumatoid arthritis experience morning stiffness that lasts 1 hour or longer. Characteristic subcutaneous nodules and other extra-articular disease manifestations including interstitial lung disease, vasculitis, and various forms of inflammatory eye disease are markers of severe disease.

Arthritis in general, and rheumatoid arthritis in particular, is a common cause of disability. More than a third of patients eventually experience work disability because of the disease.[3] The loss of ability to maintain employment begins early after disease onset; 80% of patients are working at 2 years, and 68% are working at 5 years.[4] Life expectancy is shortened by up to 3 to 5 years, especially in patients with extra-articular disease and those who develop serious treatment-related adverse effects including infections, tumors, and gastrointestinal toxicity from drugs used to treat rheumatoid arthritis.[5,6] Furthermore, patients with rheumatoid arthritis are at 50% greater risk of heart attack and more than 2-fold increased risk of heart failure.[7-11]

A major advance in management of rheumatoid arthritis is the recognition that early diagnosis and prompt aggressive treatment substantially improve patient functional outcome and morbidity. The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria for rheumatoid arthritis represent an improvement in the diagnostic approach to the disease.[12] These organizations have recognized that older criteria are insufficient to differentiate patients in whom rheumatoid arthritis eventually will develop from those in whom arthritis will have a limited course. Patients classified as having rheumatoid arthritis according to the previous criteria already have established and advanced disease. The new criteria promote the goal of early intervention to improve outcomes, prevent joint damage, and limit functional decline.

Recently, the ACR[13] and the EULAR[14] have published evidence-based recommendations for management of rheumatoid arthritis. However, these general guidelines permit considerable leeway for interpretation and in themselves are not sufficient for rheumatologists to use to devise a practical and standardized management approach. This clinical review describes our management approach, assimilating the current evidence, expert opinion, and clinical experience. It is intended to serve as a pragmatic approach for use in the treatment and management of rheumatoid arthritis.

TREATMENT PRINCIPLES

Goals of Therapy

The goal of present-day therapy for rheumatoid arthritis is to control the underlying inflammatory disease. Attainment of this goal will alleviate pain,

restore patients' quality of life, and ultimately, preserve their independence and ability to perform activities of daily living and vocational and avocational pursuits. Major long-term goals of treatment are to prevent joint destruction and prevent comorbidities of disease and treatment, including heart disease and osteoporosis.

Early Referral and Diagnosis

Timely intervention and accurate diagnosis reduce the burden of disease and the progression of rheumatoid arthritis, with the result that outcomes have globally improved, with more patients able to work and less need for joint reconstructive surgery than in previous decades. The expectations for disease management have become more rigorous as the effects of the disease have become better understood and treatments have improved. Critical to these expectations has been a fundamental change in the mindset of rheumatologists and their patients, who now expect complete abrogation of disease activity and remission or near remission as treatment goals.

The classification of "definite rheumatoid arthritis" is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better accounts for the synovitis, and a score of 6 or higher in 4 individual score domains (Table 1).[12,15] These domains and their score ranges are as follows: number and site of involved joints (0-5), serologic abnormality (0-3), increased acute-phase response (score, 0-1), and symptom duration (2 levels; score, 0-1). They incorporate the more specific anti–citrullinated protein antibody (ACPA; formerly, anticyclic citrullinated peptide antibody) serologic test, which has high specificity (>90%) and moderate sensitivity (~60%) for rheumatoid arthritis. Rheumatoid factor may also be used as a serologic marker of the disease, although it has considerably lower specificity (<70%), with comparable sensitivity as ACPA, which increases to about 80% percent with prolonged disease.

Application of these new criteria facilitates earlier referral of patients with early inflammatory arthritis to rheumatologists and earlier diagnosis of rheumatoid arthritis. For example, patients with early-morning stiffness, a swollen wrist joint, and strongly positive ACPA test results for 6 weeks (or less with an abnormal C-reactive protein [CRP] concentration) fulfill the criteria for rheumatoid arthritis, and disease-modifying therapy should be initiated. We advocate use of "early arthritis clinics" or, at the least, triage of appointment indications so that patients with suspected early rheumatoid arthritis can be seen in urgent appointment slots within 1 to 2 weeks of referral.

In some patients with early rheumatoid arthritis, clinical examination may not yield evidence of synovitis, in particular in those who test seronegative for the disease. Advanced imaging techniques such as high-resolution ultrasonography and magnetic resonance imaging can be useful in such cases. Identification of synovitis, bone edema, and bone erosions not evident at clinical examination alone can facilitate early diagnosis when these findings otherwise support clinical judgment.[16-19]

Assessment of Disease Activity

Clinical evaluation of rheumatoid arthritis should include quantitative assessment of disease activity, and treatment decisions should hinge on this assessment.[13,14] Routine evaluation includes assessment of patient-reported outcomes including pain, the patient Global Assessment of Disease Activity score, and the Health Assessment Questionnaire Disability Index score. The physician, trained nurse, or physician assistant performs the evaluator global assessment. These assessments are performed using visual analog scales, either in paper or electronic format. The evaluator also physically examines the joints and evaluates the number of tender and swollen joints on the basis of the 28-joint count, which includes the proximal interphalangeal joints (first through fifth), metacarpophalangeal joints (first through fifth), wrists, elbows, shoulders, and knees, on both sides of the body.[20] We also routinely assess the serum CRP concentration, which is the most clinically useful biomarker.[21] We prefer the CRP concentration to the sedimentation rate because the test is simple, more reliable, and not age dependent. Measurement of both acute-phase reactants offers no additional clinical value.[22] A list of our standard clinical assessment tools is provided in the Supplemental Table (available online at http://www.mayoclinicproceedings.com).

Composite measures of these individual factors should be used to determine the absolute state of clinical disease activity.[13,14] Such composite measures are more sensitive to changes in disease activity than are the aforementioned individual assessments.[23] Care driven by aggressive treatment modification to achieve targets based on a composite disease activity score, such as the Disease Activity Score, leads to superior clinical outcomes.[24,25] The Disease Activity Score using 28 joint counts (DAS28) is recommended by EULAR for assessing disease activity and treatment response.[20,26,27]

The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) are alternative composite disease activity measures that have salutary advantages in clinical practice.[28] These measures do not require any calculation based on a complicated formula, and the CDAI does not require measurement of an acute-phase reactant.[29,30] The SDAI and CDAI provide a more stringent defi-

TABLE 1. 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis[a]

Variable	Score
Target population: Who should be tested?	
Patients who have at least 1 joint with definite clinical synovitis (swelling)[b]	
Patients with synovitis not better accounted for by another disease[c]	
Classification criteria for RA (score-based algorithm: add score of categories A-D. A score ≥6/10 is needed for definite classification)[d]	
A) Joint involvement[e]	
1 large joint[f]	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)[g]	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints, including at least 1 small joint[h]	5
B) Serologic findings (at least one test result is needed for classification)[i]	
Negative RF *and* negative ACPA	0
Low positive RF *or* low positive ACPA	2
High positive RF *or* high positive ACPA	3
C) Acute phase reactants (at least one test result is needed for classification)[j]	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D) Duration of symptoms (wk)[k]	
<6	0
≥6	1

[a] ACPA = anti-citrullinated protein antibody; ACR = American College of Rheumatology; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; RF = rheumatoid factor; ULN = upper limit of normal.

[b] The criteria are for classification of new patients. In addition, patients with erosive disease typical of RA with a history compatible with fulfillment of the 2010 criteria should be classified as having RA. Patients with long-standing disease including those with inactive disease (with or without treatment) who, on the basis of retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

[c] Differential diagnoses vary among patients with different clinical findings but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear which relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

[d] Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed, and the criteria might be fulfilled cumulatively over time.

[e] Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to location and number of involved joints, with placement in the highest category possible on the basis of pattern of joint involvement.

[f] Large joints include shoulders, elbows, hips, knees, and ankles.

[g] Small joints include the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

[h] In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints and other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular joints).

[i] Negative refers to international unit values that are less than or equal to ULN for the laboratory and assay; low positive refers to international unit values that are higher than ULN but 3 times ULN or less for the laboratory and assay; high positive refers to international unit values that are more than 3 times ULN for the laboratory and assay. When RF information is available only as positive or negative, a positive result should be scored as low positive for RF.

[j] Normal or abnormal is determined by local laboratory standards.

[k] Patient self-report of duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

From *Arthritis Rheum*,[12] with permission.

nition of clinical remission.[31,32] As defined by power Doppler ultrasonography, achievement of remission according to the SDAI signifies true lack of joint inflammation more accurately than with the DAS28.[33] Further, the SDAI is among the most sensitive to change in the various composite measures of disease activity, which justifies use of this measure to evaluate response.[23]

We use the SDAI primarily in defining treatment response and remission (Table 2). The SDAI should be used in patients with a history of increased CRP concentration, and the CDAI may be used in patients with repeatedly undetectable CRP concentration (<0.3 mg/dL; to convert CRP mg/dL value to nmol/L, multiply by 95.24). Systematic monitoring of these disease activity measures provides a longitudinal view of treatment effects and outcomes, which will greatly facilitate evaluation of the success of our treatment approach for managing rheumatoid arthritis.

Treat-to-Target Principle

A recent consensus statement by the EULAR indicated that the primary target of therapy in rheumatoid arthritis is remission, defined as absence of signs or symptoms of inflammatory disease activity.[14,34] Remission is a realistic and achievable target in the current era of rheumatoid arthritis therapy, in particular when treat-to-target strategies are used and when the disease is diagnosed and treated early in its course.[35-38] Use of a tight-control treatment strategy, with the goal of a DAS28 score lower than 2.6, leads to faster and more frequent remission than does treatment according to current "usual" clinical care.[25]

The ACR and EULAR have recently published more stringent criteria for remission.[39] Rheumatoid arthritis now is defined as in remission when the number of tender joints, swollen joints (both using 28-joint counts), CRP concentration (in milligrams per deciliter), and patient global assessment (on a 10-cm visual analog scale) are all 1 or less, or, alternatively, when the SDAI score is 3.3 or lower. In a relevant post hoc analysis of the ASPIRE (Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset) trial, achievement of remission (SDAI ≤3.3 or CDAI ≤2.8) by week 14 was predictive of radiographic nonprogression at 1 year, irrespective of therapy with methotrexate (MTX) alone or in combination with infliximab.[40]

Remission may not be attainable in all patients, in particular those with established disease that has been refractory to many therapies. There is also uncertainty about the validity of the remission criteria in clinical practice inasmuch as they were designed for use in clinical trials.[41]

In view of this dilemma, the EULAR guidelines acknowledge that an alternative target that is more viable in clinical practice is low disease activity,[14] as defined by an SDAI score of 11 or lower or CDAI score of 10 or lower. Patients who achieve this target overall do well and have low mean progression of joint damage, especially those patients receiving biologic therapy.[40] However, we are concerned that uncritical use of the remission target might lead to overtreatment and inappropriate exposure of some patients to expensive and potentially risky biologic therapies. Although remission is the most appropriate target in the long term, we recognize that physicians must individualize treatment goals on the basis of prognostic characteristics and patient preferences.

TABLE 2. Composite Disease Activity Measurement[a,b]

Formulas for calculation of recommended composite measures

SDAI = TJC + SJC + PGA + EGA + CRP

CDAI = TJC + SJC + PGA + EGA

Disease activity cutoffs

	Absolute disease activity level			
Index	Remission	Low	Moderate	High
SDAI	≤3.3	≤11	≤26	>26
CDAI	≤2.8	≤10	≤22	>22

[a] CDAI = Clinical Disease Activity Index; CRP = C-reactive protein (mg/dL); EGA = Evaluator Global Assessment (0-100 mm); PGA = Patient Global Assessment (0-100 mm); SDAI = Simplified Disease Activity Index; SJC = No. of swollen joints using a 28-joint count; TJC = No. of tender joints using a 28-joint count.

[b] Measurement of disease activity at each point in time should be based on quantitative assessments and summarized using a composite disease activity instrument. We use the SDAI for patients with increased acute-phase reactant levels, and for all others we use the CDAI. Note that the SDAI requires that CRP values be given in milligrams per deciliter. When calculating the SDAI for a patient with CRP reported as less than the detectable range (ie, <0.3 mg/dL), we input a value of 0.29 for the calculation. To convert CRP mg/dL value to nmol/L, multiply by 95.24.

Adapted from *Best Pract Res Clin Rheumatol*,[28] with permission.

Assessment of Disease Severity and Prognosis

The clinician must assess the probability of disease progression and of complications in patients with rheumatoid arthritis. At diagnosis, useful predictors of severe disease and poor prognosis include positive results of blood tests for rheumatoid factor and/or ACPA, greater disability, increased acute-phase reactant concentrations, and presence of radiographic joint erosions at baseline. The presence of rheumatoid factor, ACPA, or the major risk allele for rheumatoid arthritis, the human leukocyte antigen *DRB1* "shared epitope," is not useful for predicting treatment response in the context of current treatment approaches.[42] Tobacco smoking is a modifiable predictor of adverse outcomes.[43-46]

There is some evidence that clinical prediction tools might be useful in assessing the risk of radiographic disease progression[47,48]; however, we do not advocate use of these in clinical practice at this time. The role of commercially available biomarker panels remains to be defined. Development of more useful biomarkers for predicting treatment response and the likelihood of adverse outcomes in personalized treatment strategies will advance the management of rheumatoid arthritis.

Nonpharmacologic Principles

Consideration of nonpharmacologic principles is crucial, in our opinion, to optimal management of rheumatoid arthritis. Education of patients about the pathophysiologic characteristics of the disease, self-management skills, and principles of joint protection lead to improved health and physical function.[49,50] Occupational therapy, in particular, is beneficial for instruction about joint protection and prescription of assistive devices, orthotics, and splints, which can substantially improve function and reduce pain.[51-53] We advise patients that adequate rest reduces fatigue associated with active rheumatoid arthritis and that resting joints during periods of poorly controlled inflammation will lessen the symptoms of the disease. Cognitive behavioral therapy can also benefit patients with fatigue by enhancing self-management and reducing their sense of helplessness.[54] Dynamic exercise programs that incorporate both aerobic exercise and progressive resistance training improve fitness and strength, have salutary benefits on lean body mass, and are safe.[55,56] All of these approaches to patient management are best undertaken in a patient-centered manner by a multidisciplinary care team that includes a rheumatologist, nurses, physical and occupational therapists, psychologists, and a skilled primary care physician.

TREATMENT APPROACH

Initial Treatment Approach

There is a strong rationale for MTX monotherapy for newly diagnosed rheumatoid arthritis (Figure 1). A recent 3E Initiative Consensus Group recommendation (No. 7) states that in patients who are naïve to disease-modifying antirheumatic drugs (DMARDs),

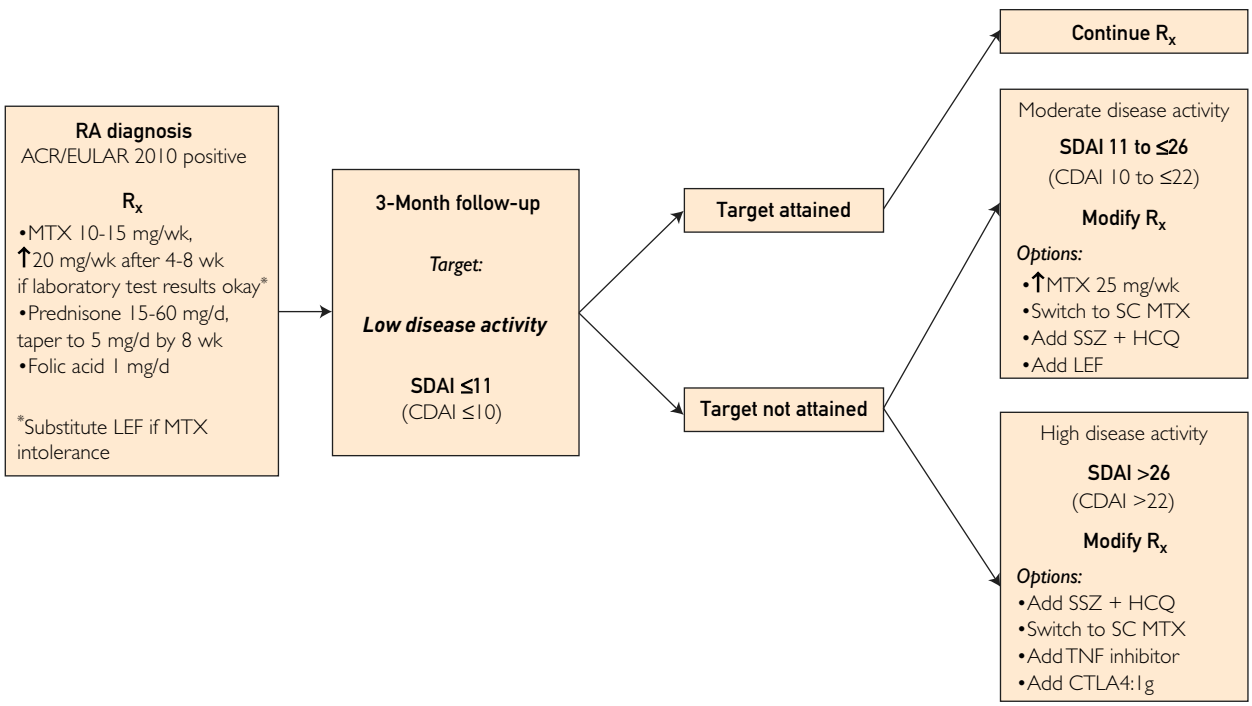

FIGURE 1. Our treatment approach to newly diagnosed rheumatoid arthritis (RA) from baseline to 6 months of follow-up. ACR/EULAR 2010 = American College of Rheumatology/European League Against Rheumatism 2010 Classification Criteria for RA; CDAI = Clinical Disease Activity Index; CTLA4:Ig = cytotoxic T lymphocyte–associated antigen 4:immunoglobulin fusion protein; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; R_x = prescription; SC = subcutaneous; SDAI = Simplified Disease Activity Index; SSZ = sulfasalazine; TNF = tumor necrosis factor.

"the balance of efficacy/toxicity favours methotrexate monotherapy over combination with other conventional DMARDs."[57] This conclusion is supported by a 2010 Cochrane systematic review that emphasized lack of evidence of a statistically significant advantage for initial combination therapy using MTX and other conventional DMARDs over monotherapy with MTX.[58]

A number of randomized, placebo-controlled clinical trials have tested the efficacy and safety of MTX, biologic agents (including various tumor necrosis factor [TNF] inhibitors or the T-cell costimulation blocker cytotoxic T lymphocyte–associated antigen 4:immunoglobulin fusion protein [CTLA-4:Ig]), or their combination, in patients with early MTX-naïve rheumatoid arthritis including many with poor prognostic signs.[37,59-64] The results of these studies suggest that the combination of MTX with a TNF inhibitor or CTLA-4:Ig (abatacept) has greater efficacy than MTX monotherapy insofar as both clinical and radiographic outcomes are concerned.

In our opinion, these trials have a number of limitations. Disease severity in patients participating in clinical trials is systematically different from that in patients we see in the outpatient clinic. In many studies, treatment with MTX, TNF inhibitors, or other biologic agents, or combinations thereof, is administered according to fixed protocols that do not reflect longitudinal clinical care, which often requires modification of the treatment regimen sooner than is typically permitted in trials with patients in whom the disease fails to improve sufficiently. Influential to our thinking is the TEAR (Treatment of Early Aggressive Rheumatoid Arthritis) trial, an investigator-initiated, randomized, double-blind, placebo-controlled trial of 4 treatment strategies, performed in the United States, that compared not only initial monotherapy vs combination therapy but also treatment with conventional DMARDs vs a TNF inhibitor (etanercept), published thus far in abstract form.[65,66] The results of this trial do not support any advantages of initial combination therapy incorporating etanercept in either clinical or radiographic outcomes at 2 years over initial MTX monotherapy with step-up to combination therapy at 6 months because of inadequate response.

The likely response to MTX cannot be reliably predicted on the basis of current clinical assessments.[67] Certainly, practical and cost considerations favor initial MTX therapy over combinations of DMARDs or biologic agents. Thus, at this time, we favor MTX therapy in most patients unless there are contraindications. Our approach is to initiate MTX at a dose of 15 mg/wk along with folic acid at 1 mg/d. Lower doses of MTX are required in some elderly patients and in patients with chronic kidney disease. Folic acid supplementation reduces mucosal and gastrointestinal toxicity, and likely liver toxicity, without reducing MTX efficacy.[68]

Numerous clinical trials have reported the salutary benefits of high-dose prednisone therapy in early rheumatoid arthritis. Two European studies, COBRA (Combination Therapy in Rheumatoid Arthritis) and BeSt (Behandel-Stratieën) trial, found that a high-dose oral prednisone regimen (60 mg, tapering to 7.5 mg by week 6, then stopping after week 12) in combination with other conventional DMARDs substantially inhibited the progression of radiographic joint damage, and this effect was sustained over many years.[35,69] In particular, the BeSt study findings suggest that the addition of high-dose prednisone therapy may mitigate the advantage of initial biologic therapy, in this case with infliximab, further supporting our approach of not using a biologic agent initially. To date, no studies have evaluated a more intermediate starting dose (ie, 20 mg/d).

Considering the known association of higher dosages with increased risk of opportunistic infections, as well as problems with tolerability in some patients, our approach is to individualize the initial prednisone dosage on the basis of disease activity, metabolic factors (ie, diabetes mellitus), and patient risk factors for infection and osteoporosis. Our approach to the use of prednisone is supported by evidence that the disease-modifying and erosion-inhibiting benefits of low-dose oral prednisone therapy (5-10 mg/d) are sustained for at least 2 years, with minimal corticosteroid-related adverse effects.[70,71] Because most of the benefit is in the first year, our recommendation is to continue prednisone at 5 mg/d for 6 months to 1 full year before gradually tapering in decrements of 1 mg every 2 to 4 weeks. It is likely that treatment using low-dose prednisone may increase the probability of a successful outcome of MTX therapy.

Critical Time Point

Low disease activity, as defined using various composite measures, is established as an important therapeutic target in early rheumatoid arthritis on the basis of findings of the TICORA (Tight Control of Rheumatoid Arthritis) and BeSt trials.[36,60] The absolute disease activity state, either low disease activity or remission, as defined by the SDAI, has been found in a meta-analysis of biologic therapy to be strongly predictive of the probability of remission at 1 year irrespective of initial MTX monotherapy or combination therapy with TNF inhibitors.[72] Not many more patients achieve remission at 6 months than at 3 months. Overall, more than 75% of patients with low disease activity or remission at 3 months are in remission at 1 year. It is our view that

3 months after initiation of therapy is the most useful time to assess the probability of attaining clinical remission at 1 year (Figure 1).

Patients in whom initial MTX therapy, optimized to 20 to 25 mg/wk or more (or a maximally tolerated oral or subcutaneous dosage), along with prednisone therapy (starting with an initial moderate dose and tapered to 5 mg/d by week 8), does not result in low to moderate disease activity by 3 months are unlikely to achieve long-term remission of disease by 6 to 12 months without treatment modification. These patients are at substantial risk of continued radiographic joint destruction. The importance of treating to this defined target at 3 months is supported by the finding that therapy driven by disease activity score vs routine care leads to higher rates of remission and lower rates of radiographic progression of disease.[24,73]

We make separate treatment recommendations for patients with moderate vs high disease activity at 3 months (Figure 1). The results from the BeSt and SWEFOT (Swedish Farmacotherapy) trials indicate that step-up therapy using sulfasalazine (SSZ) and hydroxychloroquine (HCQ) in these patients is inferior to the addition of a TNF inhibitor.[60,74,75] In contrast, the results of the TEAR trial suggest that step-up treatment using SSZ and HCQ is comparably effective to step-up etanercept therapy in both clinical response and radiographic outcomes.[65,66]

To mitigate this apparent contradiction, we have considered data regarding the probability of remission at 1 year on the basis of absolute disease activity at 3 months. Patients in whom moderate, but not low, disease activity (SDAI >11 but ≤26) has been achieved at 3 months have an indeterminate probability of low disease activity or remission at 1 year.[72] Thus, we advocate more conservative treatment modifications in this group at 3 months. Options include increasing the MTX dose to 25 mg/wk orally, switching to subcutaneous MTX, adding SSZ and HCQ (triple therapy), and less commonly, adding leflunomide.

In patients with high disease activity (SDAI >26 or CDAI >22) at 3 months that is refractory to treatment with optimized MTX and prednisone, the probability of attaining remission at 1 year is low without addition of combination therapy or a biologic response modifier.[36,60,72,74] In this setting, both TNF inhibitors[59,62,76-78] and abatacept[79] are approved and are recommended biologic response modifiers for step-up treatment. Although interleukin 1 receptor antagonist therapy (anakinra) is approved for treatment in this context, we regard this medication as generally less effective than the above-mentioned agents, and, thus, cannot recommend its use at this disease stage.

The results of the TEAR study suggest that step-up therapy with SSZ and HCQ in addition to MTX as late as 6 months is similarly effective as step-up therapy with a biologic agent in this group at high risk; thus, on the basis of available evidence, triple-DMARD therapy may be a reasonable option in some patients. A caveat is the need to reevaluate this recommendation after full publication of the TEAR study results.

Six to 12 Months of Disease

Attainment of minimal disease activity is an important goal, and one that is of particular consequence to achieve by 1 year after diagnosis. Patients in the FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) study who did not achieve remission by 1 year experienced a substantially higher rate of progression of joint erosions over the ensuing decade than did patients who did achieve remission.[80] Combination regimens are markedly more likely than monotherapy regimens to induce remission.[81] The window of 6 to 12 months is chosen because in patients in whom biologic therapy was initiated at 3 months, up to 6 months may justifiably be required before the treatment response can be definitively assessed.

In our practice, treatment is intensified in patients with an SDAI score higher than 11 (CDAI >10) at 6 to 12 months (Figure 2). In patients receiving MTX monotherapy, treatment should be escalated either with the addition of SSZ and HCQ for triple-DMARD therapy or the addition of TNF inhibition or T-cell costimulation blockade (abatacept). In patients already receiving combined MTX plus biologic therapy (either a TNF inhibitor or abatacept), treatment with an alternative biologic response modifier should be initiated. Abatacept is more effective than placebo in patients with inadequate response to TNF inhibitors[82] and has a good safety record.[83]

A single trial of switching to another TNF inhibitor is appropriate and can be effective; however, additional trials of anti-TNF agents are not likely to be so beneficial as switching to a drug with an alternative mechanism of action.[84,85] At this early stage of disease, we favor TNF inhibitors or abatacept over other biologic agents, although anti-CD20 (rituximab)[86,87] and anti-interleukin 6 receptor monoclonal antibody (tocilizumab)[88,89] therapies are effective and safe for treatment of rheumatoid arthritis with inadequate response to one or more TNF inhibitors. These agents can also be considered under individual circumstances, depending on comorbidities and previous treatment responses.

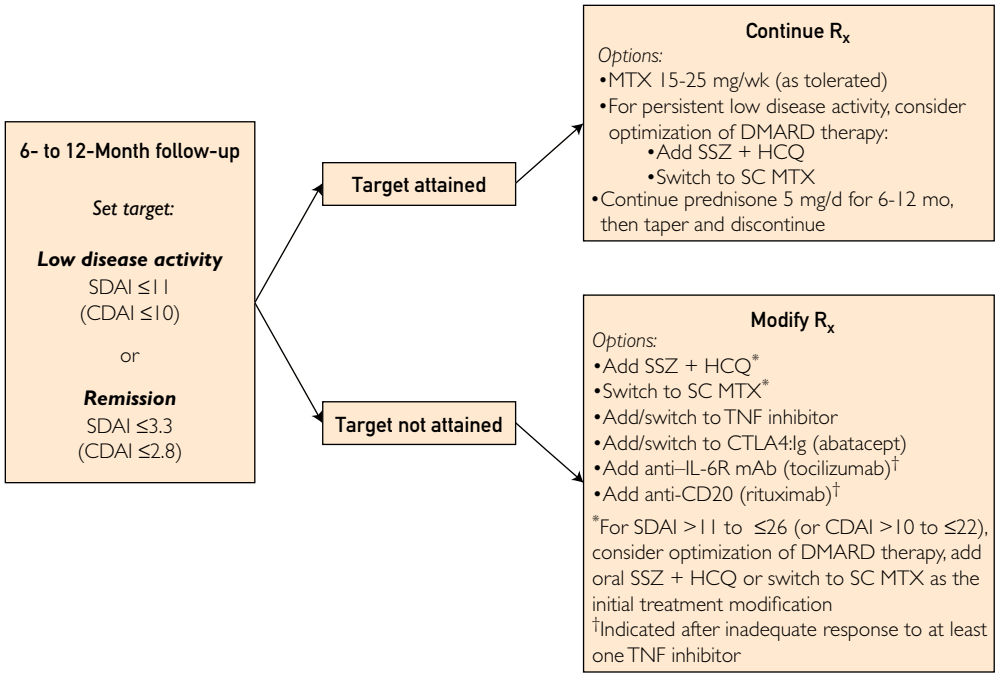

FIGURE 2. Our treatment approach to early rheumatoid arthritis (RA) from 6 months to 1 year. anti–IL-6R = anti-interleukin 6 receptor; CDAI = Clinical Disease Activity Index; CTLA4:Ig = cytotoxic T lymphocyte–associated antigen 4:immunoglobulin fusion protein; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; mAb = monoclonal antibody; MTX = methotrexate; R_x = prescription; SC = subcutaneous; SDAI = Simplified Disease Activity Index; SSZ = sulfasalazine; TNF = tumor necrosis factor.

Beyond the First 6 to 12 Months of Disease

Beyond the first year, patients with persistently moderate to high disease activity despite treatment according to the recommended algorithm are at substantial risk of disease progression. Although we consider low disease activity an acceptable goal, we strongly recommend ongoing efforts to tailor the treatment regimen toward complete abrogation of joint inflammation. At this point, the MTX dose should be increased to 20 to 25 mg/wk or the maximal tolerated dosage, then switched to subcutaneous parenteral administration as needed. Assessment of MTX metabolites may offer some insight as to bioavailability. Patients with inflammatory activity predominantly in single isolated joints should receive local intra-articular glucocorticoid injection.

In our recommendations for patients with active disease at this point, we consider patients receiving single-drug or combination DMARD therapy separately from patients receiving biologic response modifiers (Figure 3). In patients receiving DMARD-only therapy, either triple-DMARD therapy should be initiated, adding SSZ and HCQ to optimize MTX therapy, or a TNF inhibitor or CTLA-4:Ig (abatacept) should be added to MTX therapy. In patients receiving a biologic agent, either the particular biologic agent should be discontinued on initiation of triple-DMARD therapy or treatment using an alternative biologic agent, preferably one with an alternative mechanism of action, should be started.

In our view, any new treatment usually should be tried for at least 3 to 6 months to fully assess its efficacy. No studies to date have compared the efficacy of various therapeutic strategies one-on-one using randomized, double-blind, placebo-controlled designs. In addition, few biomarkers are yet available to guide management of individual patients. An exception is the presence of rheumatoid factor, antibodies to citrullinated protein, or increased serum IgG concentration, all of which are generally predictive of a favorable response to rituximab.[90] A biomarker of usefulness in our practice is to recommend abatacept or tocilizumab rather than rituximab in patients who test seronegative for rheumatoid factor and with inadequate response to one or more anti-TNF drugs.

Mayo Clin Proc. ■ July 2012;87(7):659-673 ■ http://dx.doi.org/10.1016/j.mayocp.2012.03.011
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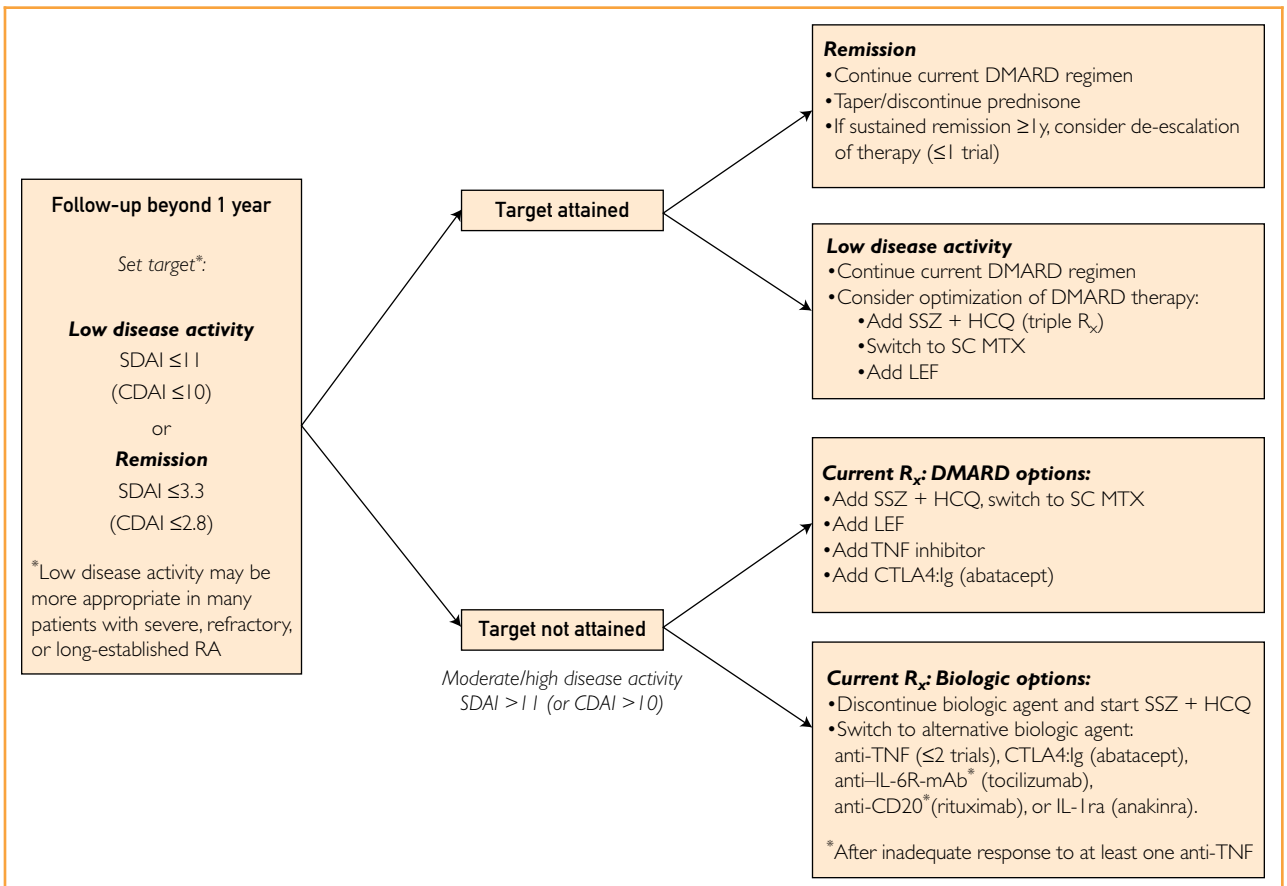

FIGURE 3. Our approach to treatment of rheumatoid arthritis (RA) beyond the first year of disease. DMARD therapy refers to use of methotrexate (MTX) and other conventional disease-modifying antirheumatic drugs. Biologic therapy refers to treatment with tumor necrosis factor (TNF) inhibitors, abatacept, rituximab, tocilizumab, or anakinra. anti–IL-6R = anti-interleukin 6 receptor; CDAI = Clinical Disease Activity Index; CTLA4:Ig = cytotoxic T lymphocyte–associated antigen 4:immunoglobulin fusion protein; HCQ = hydroxychloroquine; IL-1ra = interleukin 1 receptor antagonist; LEF = leflunomide; mAb = monoclonal antibody; R_x = prescription; SDAI = Simplified Disease Activity Index; SSZ = sulfasalazine.

Findings of recent studies suggest that in a small number of patients managed using the treat-to-target strategy, therapy can be tapered successfully, and even sustained drug-free remission can be achieved in as many as 15% to 25%.[91,92] Although these patients may experience a flare-up of disease after observation for 3 to 6 months, in most, clinical remission is achieved again with resumption of therapy and there is no radiologic progression of disease.[91] Shorter symptom duration, absence of rheumatoid factor or ACPA, lower mean disease activity before remission, and less baseline disability are associated with attainment of sustained drug-free remission.[92,93]

After the first 1 to 2 years, the benefits of long-term corticosteroid therapy are often outweighed by the risks, including cataracts, osteoporosis and fractures, and potentially, cardiovascular disease. Beyond the early disease period, prednisone therapy primarily provides symptom relief and does not modify the course of disease progression. The most recent EULAR guidelines for cardiovascular risk management in patients with rheumatoid arthritis recommend using the lowest possible prednisone dosage.[94] From the recent 2010 recommendations for prevention of glucocorticoid-induced osteoporosis, it is clear that there is no "safe" dosage of prednisone insofar as bone density and structure are concerned.[95] Thus, beyond the first 1 to 2 years of disease, the use of prednisone should be primarily as bridge therapy for flare-ups while awaiting the efficacy of nonbiologic and biologic DMARD therapy. Attempts should be made in all patients to gradually taper and eventually discontinue glucocorticoid therapy before accepting long-term low-dose prednisone therapy.

Potential Pitfalls and Alternative Approaches

No treatment approach or guidelines can ever encompass all scenarios relevant to clinical practice adequately; we firmly acknowledge this truth. The judgment of the primary rheumatologist is of paramount importance in cost-effective, appropriate, and safe implementation of our treatment recommendations. Biomarkers such as CRP and composite disease activity measures such as the SDAI and CDAI augment clinical judgment. Experienced clinicians recognize the limitations of composite measures at both the high and low ends of the scale. For example, patients with fibromyalgia can have high disease activity scores because of high tender joint counts and patient global assessment in the absence of swollen joint counts or elevated acute phase reactant levels.[96] In patients with disease remission according to composite measures, active joint inflammation can, nonetheless, be detected with high-resolution imaging.[97-99]

The art of medicine is alive and well in rheumatology. Patients with rheumatoid arthritis can experience central pain amplification yet have active inflammation. When joint tenderness, fatigue, and subjective disease activity are disproportionate to the provider assessments of disease activity, the response should not be to follow our approach according to the calculated SDAI and initiate therapy with, for example, biologic agents. Rather, the provider should investigate the cause of the symptoms. For example, noninflammatory causes of pain such as regional musculoskeletal pain syndromes or osteoarthritis should be identified and treated accordingly.

Magnetic resonance imaging or high-resolution ultrasonography with power Doppler examination could be considered to identify evidence of subclinical inflammation that might be clinically relevant, for example, in predicting progression of erosive disease.[97,100] Discrepancy between the provider and patient in assessment of disease activity should be addressed, because this discordance is associated with increased symptoms of depression and reduced quality of life.[101] Widespread chronic pain due to central pain amplification in the absence of active inflammatory disease might be treated using pharmacologic and nonpharmacologic approaches. Comorbid depressive or anxiety disorders should be treated in conjunction with our colleagues in psychiatry and pain management.

RECOMMENDATIONS

Contemporary management of rheumatoid arthritis emphasizes early diagnosis, quantitative monitoring of disease activity, and intensive goal-directed therapy to achieve the best possible outcomes for patients. The major goal of treatment is to abrogate the inflammatory disease activity and achieve long-term remission, which in the future ideally will mean absence of disease and minimal need for medications. Application of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis facilitates early diagnosis, which is critical to the highest probability of clinical remission with disease-modifying therapy. Our treatment approach is to use MTX plus prednisone as the initial treatment. Three months is the critical time at which we assess the response to MTX and consider step-up to combination treatment strategies.

Our treatment approach reflects several gaps remaining in our understanding of the best practices for the management of rheumatoid arthritis. We do not know how best to measure disease activity and to assess the clinical response to treatment. This can create uncertainty in decision making about treatment. The benefits and limitations of targeting low disease activity vs remission are still to some extent uncertain. The relative benefits and harms of emphasizing initial prednisone use vs initial biologic therapy remain largely unexplored. The effects of treatment on the risk of developing comorbidities such as cardiovascular disease remain unclear. Current methods for predicting the efficacy and toxicity of specific treatments are imperfect, hindering us from achieving truly personalized therapy. We hope resolution of these issues will be forthcoming from clinical research studies, enabling us to improve our management approach to patients with rheumatoid arthritis.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **ACPA** = anti–citrullinated protein antibody; **ACR** = American College of Rheumatology; **BeSt** = Behandel-Strategieën [trial]; **CDAI** = Clinical Disease Activity Index; **CRP** = C-reactive protein; **CTLA-4:Ig** = cytotoxic T lymphocyte–associated antigen 4:immunoglobulin fusion protein; **DAS28** = Disease Activity Score in 28 joints; **DMARD** = disease-modifying antirheumatic drug; **EULAR** = European League Against Rheumatism; **HCQ** = hydroxychloroquine; **MTX** = methotrexate; **SDAI** = Simplified Disease Activity Index; **SSZ** = sulfasalazine; **TEAR** = Treatment of Early Aggressive Rheumatoid Arthritis [study]; **TNF** = tumor necrosis factor

Potential Competing Interests: Dr Davis is an investigator on studies with Centocor Inc, Malvern, PA; VA Cooperative Studies Program, US Department of Veterans Affairs, Washington, DC; Genentech, Inc, South San Francisco, CA; Novartis Corp, East Hanover, NJ; Rheumatoid Arthritis Investigational Network/University of Nebraska Medical Center, Omaha; and UCB Pharma, Inc, Smyrna, GA. He has received grant support or contracts from the Arthritis

Foundation, Indianapolis, IN; Centocor; Genentech; Mayo Foundation, Rochester, MN; Myriad RBM, Inc, Austin, TX; National Center for Research Resources and National Institutes of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD; Novartis Corp; UCB Pharma, Inc; and University of Nebraska Medical Center Cooperative Studies Program.

Dr Matteson is an investigator on studies with the American College of Rheumatology, Atlanta, GA; Amgen Inc, Thousand Oaks, CA; Ardea Biosciences, San Diego, CA; AstraZeneca, London, UK; Biogen Idec, Weston, MA; Centocor Inc, Malvern, PA; Eli Lily and Co, Indianapolis, IN; Genentech, Inc, South San Francisco, CA; Hoffman-LaRoche Inc, Nutley, NJ; Human Genome Sciences, Inc, Rockville, MD; Janssen Biotech, Inc, Horsham, PA; Pfizer Inc, New York, NY; Novartis Corp, East Hanover, NJ; Roche, Indianapolis, IN; Schering-Plough/Merck & Co, Inc, Whitehouse Station, NJ; and UCB Group; UCB, Inc, Atlanta, GA. He has received grant support or contracts from Amgen, Bristol-Myers Squibb, New York, NY; Centocor/Johnson & Johnson; Genentech; Mayo Foundation, Rochester, MN; Novartis; National Institutes of Health, Bethesda, MD; and Veteran's Administration, US Department of Veterans Affairs, Washington, DC. He participates as consultant/scientific advisory board member for Abbott Laboratories, Abbott Park, IL; Amgen, Biogen Idec; Centocor; Crescendo Bioscience, South San Francisco, CA; West Lafayette, IN; Horizon Pharma USA, Inc, Deerfield, IL; and Novartis.

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