



# The Role of Early, Aggressive Treatment for Rheumatoid Arthritis: A Window of Opportunity for Intervention

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This activity is supported by an educational grant  
from Genentech, Inc. and Biogen Idec.



## Target Audience

The Clinical Newsletter Series is intended for rheumatologists, rheumatology fellows, and other health care providers who are interested in or participate in the diagnosis and treatment of rheumatoid arthritis (RA) in adults.

## Educational Objectives

After completing this CME activity, participants should be able to:

- Describe the benefits of early, aggressive treatment and achievement of tight control of RA and the associated risks when treatment is delayed
- List baseline prognostic factors that can be used to identify patients at risk for early, aggressive disease to improve the stratification and subsequent treatment of patients
- Determine treatment strategies based on the aggressiveness of the disease to improve the course and outcome for patients with RA
- Describe a strategy to enhance early referral to rheumatologists by other care providers to facilitate earlier treatment of RA

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Release Date: January 2007

Expiration Date: January 2009



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## Volume 2

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Independent Contractor (Clinical Trials)	Biogen Idec, Centocor, Inc., Genentech, Inc., Human Genome Sciences, Pfizer Inc, Roche Laboratories, Inc.
Grant Support	Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb Company, Centocor, Inc., Daiichi Pharmaceutical Co. Ltd., Genentech, Inc., Merck & Co., Inc., Ortho- McNeil, Inc., Pfizer Inc, Proctor & Gamble, TAP Pharmaceutical Products, Inc., Wyeth

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## Overview

Rheumatoid arthritis is a chronic, additive, inflammatory arthropathy that affects nearly 2.5 million Americans. Treatment is best when initiated early and aggressively, with the aim of achieving remission and prevention of the damage and functional sequelae of rheumatoid inflammation. For many patients, there is a small window of opportunity early in the illness, wherein delivery of effective treatment provides the best chance for optimal patient outcomes and limited joint damage. Rheumatologic evaluation and prompt treatment is needed during this time period. Suggestions for improving early referral will be discussed in this newsletter.

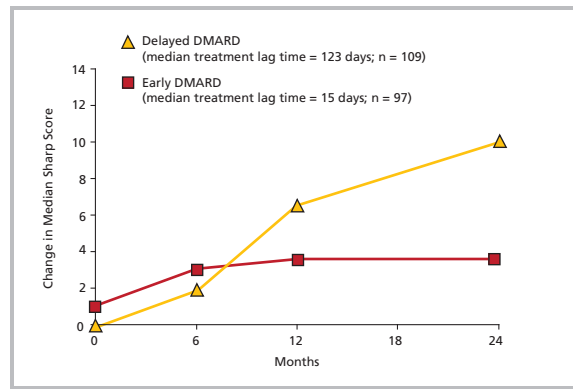
## Introduction

Significant delays in diagnosis, patient referral, and disease-modifying antirheumatic drug (DMARD) initiation still exist for many patients with new onset RA. Early presentation of these patients to a rheumatologist remains a widely unaddressed but important clinical goal.<sup>1</sup> While all rheumatologists agree on the merits of early diagnosis and aggressive treatment, few have been able to devise strategies to identify patients with early RA and facilitate early referral to the rheumatologist. A better course and outcome can be realized with early diagnosis, referral, and aggressive treatment. The rheumatologist's skill, expertise, and knowledge of advances in early RA management are essential for optimizing patient outcomes.

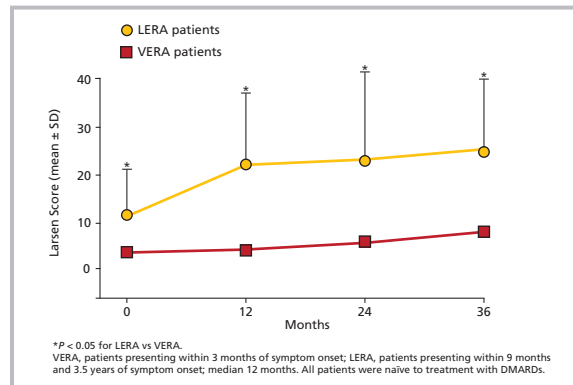
## The Case for Early Treatment: Delays in Treatment of Patients With RA Can Be Devastating

It should come as no surprise that treatment delay impacts patient outcome. This is particularly true for patients with RA, where joint destruction and disability are the consequence of untreated disease. At the time of presentation, up to 25% of patients with early RA will have evidence of radiographic erosions. In the first 2 years, this rises to more than 70% of patients.<sup>2</sup> Work disability occurs in two thirds of patients early in the disease process. Declines in Health Assessment Questionnaire (HAQ) disability scores in the first year following diagnosis predict the future loss of productivity and subsequent disability. The Norfolk registry has shown that delays in DMARD initiation beyond 6 months resulted in greater levels of disability 5 years later.<sup>3</sup> Additionally, there is a decreasing response to therapy with greater disease duration,<sup>4</sup> resulting in greater pain, damage, and physical disability.<sup>5</sup> Several studies have documented that delays in DMARD initiation of 3 to 4 months can result in substantially more radiographic damage when measured 2 years later (Figures 1–4).<sup>6–9</sup>

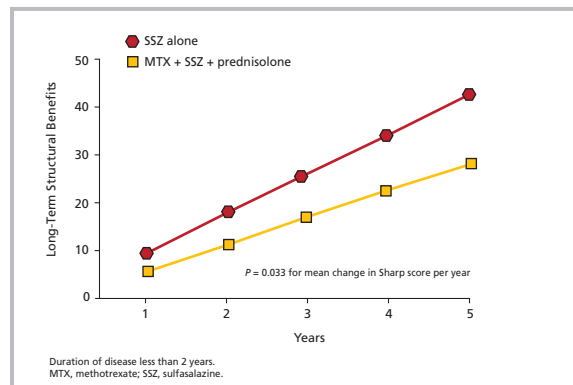
This is especially relevant in early disease, when a physician may conservatively manage patients while awaiting the results of initial diagnostic testing and treatment. Lastly, multiple large trials have shown that combination therapy is far superior to monotherapy in the management of early RA.<sup>7,9–12</sup> Hence, abundant data point to the value of early and aggressive DMARD and/or biologic use in patients with early RA. Why then are there patients with RA who do not receive aggressive therapy early in the course of disease



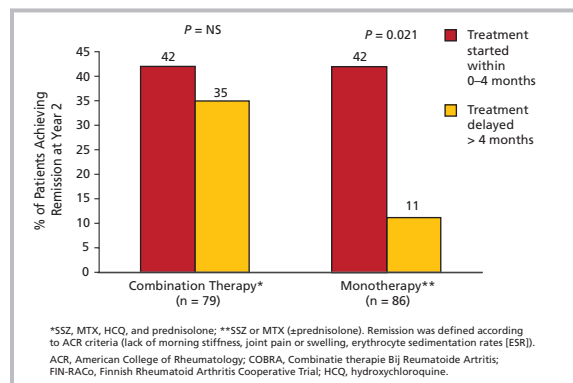
**Figure 1.** Delay in DMARD initiation results in poorer outcomes. (Reprinted from Lard LR et al. *Am J Med.* 2001;111:446-451. Copyright 2001, with permission from Elsevier.)



**Figure 2.** Very early RA (VERA) versus late early RA (LERA) impact of DMARD therapy on radiographic progression. (Reprinted from Nell VPK et al. *Rheumatology.* 2004;43:906-914, with permission from Oxford University Press.)



**Figure 3.** COBRA: step-down therapy.



**Figure 4.** FIN-RACo: impact of delaying treatment with DMARDs in early RA monotherapy versus combination therapy.

(eg, in the first 6 months)? Why are there patients with RA who have not been seen by a rheumatologist in the first 6 months of symptom onset?

## The Diagnosis and Referral of Early RA

The benefits of earlier diagnosis and timely use of drug therapy are well documented. Regardless of the drug used, earlier therapy provides a better response.<sup>4</sup> Furthermore, inducing remission promptly results in maintenance of work capacity, a benefit of great importance to both patients and society.<sup>13</sup> However, early DMARD treatment requires early referral of patients and early diagnosis of disease.

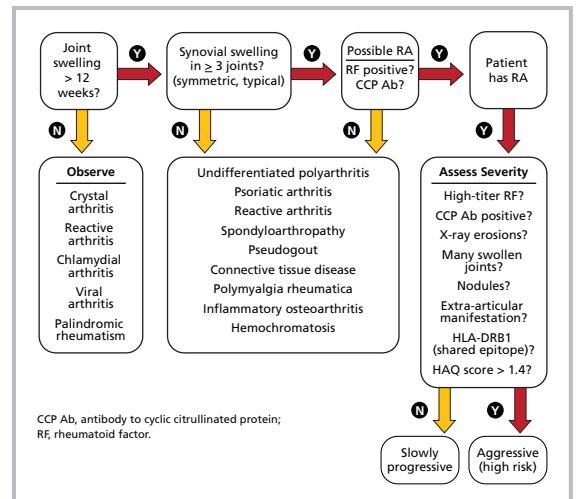
Rheumatologists have aggressively defined early RA as less than 3 months of joint symptoms.<sup>14</sup> As shown above, the earlier the diagnosis, the better it is for the patient. To make this happen, rheumatologists need to create pathways that encourage primary care physicians (PCPs) to refer their patients with RA and undifferentiated inflammatory arthritis as soon as possible. Regrettably, early diagnosis and referrals are hindered by numerous factors (Table 1).<sup>1</sup>

**Table 1.** Impediments to an Early Referral and Diagnosis

- ACR classification criteria for RA are inadequate in early RA
- Patient reluctance to seek care for nonlimiting symptoms
- Availability of over-the-counter (OTC) medications
- Inefficient use and specificity of diagnostic testing
- PCP referral inertia (“wait-and-see” approach)
- Prolonged rheumatology consultation waiting times
- Declining number of practicing rheumatologists
- Few early arthritis clinics (EACs)
- Rheumatologists not promoting their policies about early referral

The ACR classification criteria for RA were revised in 1987. Unfortunately, these were not designed for the diagnosis of early RA and are fairly insensitive in patients with disease duration of less than 12 months.<sup>15</sup> In practice, recognition of early RA is usually based on a combination of clinical features and laboratory and imaging studies as well as by the exclusion of other disorders that may mimic RA (Figure 5).<sup>16</sup> While early RA should be suspected in any patient presenting with an acute oligoarthritis or polyarthritis, the persistence (or duration) of swollen joints best predicts the development of RA.

While 6 or more weeks of symptoms are necessary according to ACR criteria, Emery and colleagues have shown that symptoms of 12 weeks or greater best predict chronicity of RA.<sup>17</sup> A definitive



**Figure 5.** Diagnosis of early RA. (Reprinted from Dao K et al. *J Musculoskeletal Med.* 2005;22:432-440. Copyright 2005, The Journal of Musculoskeletal Medicine, CMP Healthcare Media LLC. All rights reserved.)

diagnosis is best achieved by early referral to a rheumatologist. Table 2 details commonly advocated rules for early patient referral. These criteria, along with either 6 or 12 weeks of symptoms, have been shown to increase the likelihood that the patient will have RA.<sup>17</sup>

During the onset of RA, many patients may only have 1 or 2 swollen joints and be seronegative for RF or CCP antibodies. These patients are usually diagnosed as having “undifferentiated arthritis” (UA). It appears that up to 40% will go on to meet criteria for RA.<sup>18</sup> The Probable Rheumatoid Arthritis: Methotrexate Versus Placebo Treatment (PROMPT) study, an 18-month trial of 110 patients with early (< 2 years) undifferentiated inflammatory arthritis, recently demonstrated that aggressive methotrexate use resulted in fewer patients with UA evolving into RA and less overall radiographic progression.<sup>19</sup> Moreover, the ability of methotrexate to retard the evolution to RA was particularly linked to those patients with UA who tested positive for CCP antibodies, a biomarker specifically linked to the diagnosis and severity of RA.

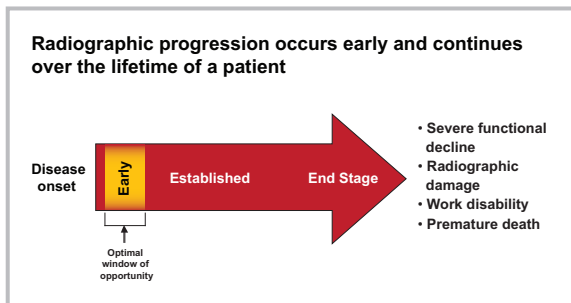
These issues underscore the challenge of identifying patients with early arthritis and treating them during this optimum window of opportunity (Figure 6).<sup>9,20</sup> The latter can be defined as a chronological period wherein effective treatment

**Table 2.** Guidelines for Referral for Early Intervention\*

- 3 or more swollen joints
- Positive metacarpophalangeal (MCP) or metatarsophalangeal (MTP) “squeeze” test to elicit pain
- Morning stiffness  $\geq$  30 minutes
- Joint symptoms  $\geq$  6 weeks but < 6 months
- Abnormal lab test: ESR, C-reactive protein (CRP), serum RF, or anticyclic citrullinated peptide antibodies (anti-CCP)

\*Any of the above is reason enough to refer a patient to an EAC.

results in optimal patient outcomes. While all physicians should recognize the need to make the earliest possible diagnosis, the greater challenge lies in facilitating early referral to the rheumatologist and early DMARD initiation.



**Figure 6.** Optimal window for treating RA.

While some studies suggest a trend toward earlier referrals to rheumatologists, the vast majority of patients with RA are not being seen in the first 6 months of symptom onset,<sup>21,22</sup> and multiple impediments to early referral and diagnosis still exist, as shown in Table 1. While some factors are patient dependent (OTC medicine use, reluctance to seek care for nonlimiting symptoms), many result from unfocused physician efforts. Foremost among these is the initial approach of PCPs for evaluating early arthritis symptoms, which is a wait-and-see approach, while early diagnostic testing and palliative therapies are employed. This approach unfortunately delays the diagnosis, referral, and DMARD initiation by several months, and many studies have clearly shown that these minor delays can result in significant damage.

Another bottleneck rests with the rheumatologists, most of whom want to see these patients and will accommodate any request to do so. However, peer-to-peer referrals for early arthritis rarely occur primarily because PCPs are unaware of the chronologic importance of symptom onset and DMARD initiation. Moreover, rheumatologists have not actively promoted their policies and pathways to facilitate early referral. Correction of these 2 factors alone would dramatically increase the number of early referrals and reduce the time to DMARD initiation in patients with early RA.

## Prognosis/Risk Assessment

The evaluation of any patient suspected of having RA should involve a baseline assessment of prognostic factors known to influence the chances of future remission or disease progression. These constitutive and activity-related clinical, laboratory, and radiographic markers have been shown to predict those who will have a more aggressive disease course.<sup>23</sup> Gossec et al demonstrated that remission at 3 and 5 years is closely correlated with 7 variables.<sup>23</sup> Practically speaking, high-risk (aggressive) disease can be defined by the presence of the following 8 risk factors (Table 3).<sup>16,23</sup>

**Table 3.** Prognostic Variables in RA

1. Many swollen joints
2. Rheumatoid nodules
3. Extra-articular manifestations
4. High titer RF
5. Anti-CCP antibodies
6. Radiographic erosions
7. HAQ score > 1.4
8. HLA-DRB1 and related alleles (the shared epitope)

Quinn and colleagues also have proposed a similar set of risk factors into their Persistent Inflammatory Symmetrical Arthritis (PISA) score.<sup>24</sup> Table 4 lists these risk factors.

**Table 4.** PISA Score Factors

- RF positivity
- Possession of the shared epitope (HLA-DR1/DR4/DR10)
- CRP level > 20 mg/L
- Female sex
- HAQ raw score > 4

Patients with a higher PISA score have been shown to have a more aggressive and damaging course.

The absence of these risk factors correlates with milder disease expression and a greater chance of spontaneous or early-treatment-induced remission. Therefore 2 different kinds of RA can be defined: aggressive RA (with a predominance of these risk factors) or slowly progressive disease (with few or no risk factors). While all patients merit aggressive care, distinguishing between aggressive and slowly progressive RA allows one to stratify high-risk and low-risk patients and to appropriately tailor a therapeutic plan for each patient.

Serologic profiling has some value as it has long been appreciated that patients with seropositive RA have a more aggressive course than seronegative patients. In addition, recent results from the PROMPT study provide evidence that the patient's serologic status during the optimum window of opportunity may influence the progression from UA to RA.<sup>19</sup> In patients with UA, early aggressive treatment with methotrexate resulted in less progression to developing RA and less radiographic joint damage. This was especially evident in patients who were anti-CCP positive.

A variety of imaging techniques may be used to assess the risk status of patients with early RA and subsequent treatment decision making. Because erosions beget erosions, their early identification may influence whether early aggressive treatment with combination DMARDs or a biologic such as a tumor necrosis factor (TNF) inhibitor is needed.



Thus, imaging can play an important role in the clinical outcome of patients.<sup>25-27</sup> Plain film radiographs are widely used and are the current standard for assessing structural outcomes in RA.<sup>28</sup> McQueen et al showed that in patients with early RA with 4 months of symptoms, 15% had erosions on x-ray but 40% had erosions on magnetic resonance imaging (MRI). The use of more sensitive tools such as ultrasound and MRI may allow for earlier detection of damage; however, their use is limited. Ultrasound is operator dependent and not widely available, and MRI is expensive and not yet validated in RA.

## Are You Undertreating or Overtreating Early RA?

Given the opportunity, rheumatologists will utilize their best treatments first to optimize patient outcomes. Many studies in early RA have shown that the first DMARD choice is most important and that earlier DMARD use establishes a lower baseline and “ceiling” from which most patients will progress over time.<sup>6,7,9</sup> Rheumatologists uniformly agree that methotrexate, in an appropriate dose, is the standard of care. While the therapeutic plan will be tailored to the severity of the disease, early treatment should begin with at least methotrexate, and other agents can be added as the markers of disease severity unfold over time. Yet some rheumatologists choose to initiate hydroxychloroquine or sulfasalazine or delay methotrexate therapy by weeks to months. In doing so, rheumatologists fail to recognize that they either undertreat or overtreat their patients with early RA. In the earliest stages, RA may be less evolved, and the use of conservative measures may be insufficient for those who will evolve into aggressive RA. Not knowing which patients will progress or have aggressive disease over time creates a conundrum for the rheumatologist. Those who espouse an aggressive approach to early disease management should subscribe to the concept of overtreatment. In this instance, overtreatment is defined as aggressively treating the patient so that disease progression can be abrogated and remission achieved. While we strive for judicious but aggressive use of DMARDs, our early DMARD choices will declare us to be undertreaters or overtreaters. Overtreatment is effective, safe, and cost-effective for the vast majority of patients with RA. Overtreatment will result in more frequent remissions, less radiographic progression, and greater functional preservation. Once remission is achieved and sustained, the physician can “step-down” or withdraw therapies as needed. If this goal is not achieved, therapy can be tailored to the disease activity and drug tolerability. Some patients may require therapies more aggressive than methotrexate alone. Figure 7 provides a treatment algorithm based on patient status and response to therapy.<sup>29</sup>

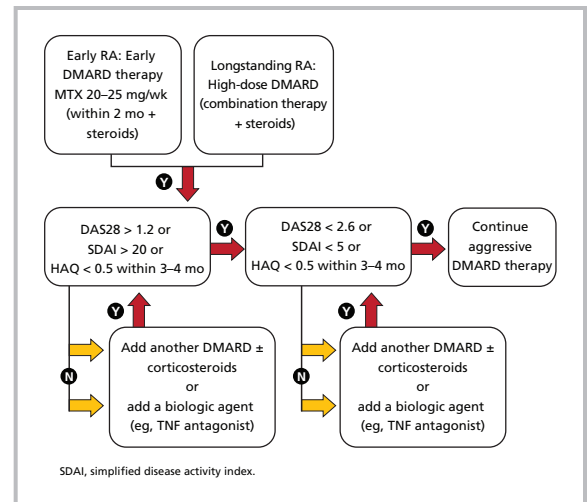


Figure 7. RA treatment algorithm: measurement possibilities and goals. (Reprinted from Smolen JS et al. *Best Pract Res Clin Rheumatol*. 2005;19:163-177. Copyright 2005, with permission from Elsevier.)

The Early Rheumatoid Arthritis (ERA) trial studied early RA (defined in this study as disease duration of 3 years or less) in patients treated more than 2 years with etanercept or methotrexate. Patients were then followed in an open-label extension study and treated with 25-mg etanercept twice weekly for an additional 3 years. In patients completing 5 years of etanercept therapy, efficacy was maintained even in patients who decreased or discontinued methotrexate or corticosteroids. In 55% of these patients, no radiographic progression occurred, and in 11% of patients, a decrease in total Sharp score was noted.<sup>30</sup>

Many clinical trials demonstrate the effectiveness of early combination therapy. For example, an initial 6-month cycle of intensive combination treatment that includes prednisolone, methotrexate, and sulfasalazine results in sustained suppression of the rate of radiologic progression in patients with early RA, independent of subsequent antirheumatic therapy.<sup>9</sup> Likewise, the FIN-RACo trial has shown aggressive combination DMARD therapy improves 5-year outcome in terms of lost productivity in patients with RA of recent onset.<sup>31</sup> Improvements were greater and much more significant in the patients who received combination therapy. Likewise, the combination of methotrexate + sulfasalazine + hydroxychloroquine was more effective than both monotherapy and the 2-drug combinations.<sup>10</sup> While one DMARD is good, two are better, and three may be optimal; however, the important point is that treatment with DMARDs must begin without delay. The recent Behandel-Strategieën (BeSt) study, however, has shown that even combination DMARD therapy early in disease is not as effective as the use of methotrexate and an anti-TNF in controlling clinical signs and symptoms.



## TNF Inhibitor Therapy in Early RA

For those patients with early RA, who do not improve with single or combination DMARD treatments, the use of biologic agents, such as TNF inhibitors, may be appropriate. TNF inhibitors are among the most effective therapies for RA, largely because they have a rapid onset of effect, improve the well-being of patients, show good response rates in clinical trials, and retard the development of radiographic erosions. Moreover, it appears that they are safe for long-term use and that serious adverse effects can be avoided with proper monitoring and screening measures.<sup>32</sup>

Numerous studies have confirmed the efficacy and safety of TNF inhibition in patients with new-onset RA. Results of the ERA, Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE), PREMIER, and BeSt studies involving etanercept, infliximab, and adalimumab have demonstrated the safety and efficacy of these agents in patients with new-onset RA.<sup>11,12,33-35</sup> These 4 large, controlled trials in early RA demonstrated: 1) ACR 20% improvement (ACR20) responses with TNF inhibitors are equivalent to, or in some cases better than, methotrexate; 2) the best responses (Disease Activity Score [DAS] remission, ACR 70% improvement [ACR70]) are achieved when TNF inhibitors are combined with methotrexate; 3) TNF inhibitors are superior to methotrexate in halting radiographic progression (especially when combined with methotrexate) (Figure 8); and 4) the safety of TNF inhibition in early RA appears to be equal to, or better than, that seen with established or severe RA. Although patients with new-onset RA should routinely receive methotrexate as their primary DMARD, TNF inhibitors may be advocated in early disease when methotrexate cannot be used and/or when the patient is at high risk for severe RA. These “high-risk” patients with RA may be identified as

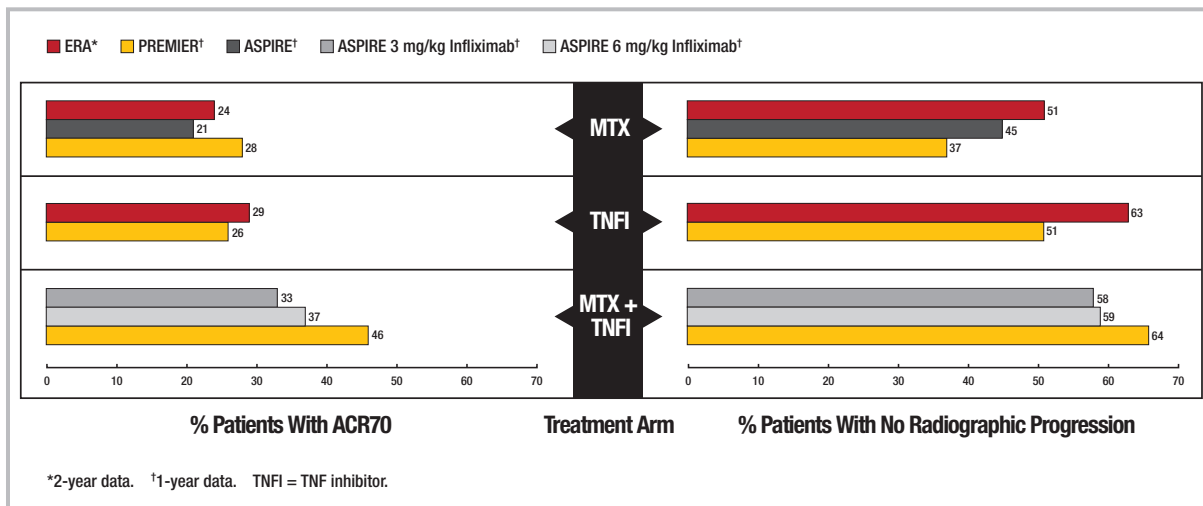
those with active polyarticular synovitis with evidence of radiographic erosions or damage and be: 1) seropositive for RF and/or CCP antibodies, 2) have functional impairment, or 3) have sustained elevations of the ESR or CRP. The identification of such high-risk patients mandates the combined use of methotrexate and TNF inhibitors, as studies have repeatedly shown the best clinical and radiographic outcomes when this combination is used instead of a TNF inhibitor or methotrexate alone.

## Facilitating Early Referral

Early referral (< 3 months) and early DMARD treatment alter the course of RA. Once the disease has become severe, it is much more difficult to treat, and improvements will not be as great as they would have been with earlier treatment. The benefits of an early arthritis referral system are summarized in Table 5.<sup>1</sup>

**Table 5.** Benefits of an Early Arthritis Referral System<sup>1</sup>

- Early referral enhances perception of a rheumatologist’s practice by both patients and PCPs and promotes the clinical services of the practice.
- Facilitated referral may attract an interesting mix of inflammatory arthropathies.
- A publicized rule-driven referral system will decrease inappropriate referrals.
- The EACs have great teaching and research potential.
- Peer-to-peer expedited referrals lead to better integrated medical care.
- Earlier rheumatology consultations result in lower health care costs
  - Fewer needless laboratory studies and radiographs
  - Appropriate use of antirheumatic medications
  - Less health care utilization overall
- Patients will have less pain, disability, articular damage.



**Figure 8.** Methotrexate and TNF inhibitors: clinical and radiographic outcomes.<sup>11,12,30,33-35</sup>

**Table 6. Models to Facilitate Early Referral**

	Description/Comments
Physician-to-physician request for expedited consultation	Routinely inform colleagues of the need to refer these patients and the referral rules (what constitutes an appropriate telephone request for expedited consultation).
Early arthritis screening clinic (staffed by nurse practitioners or physician assistants)	Can review referral documents, screen patients by telephone, and schedule new-onset arthritis referrals for intake, diagnostic assessments, and treatment using locally defined protocols.
Dedicated EAC	Often meets once weekly and is staffed by rheumatologists, with or without fellows and physician extenders. Time slots are filled by scheduling staff after being reserved for patients with early arthritis who meet entry requirements. In the absence of an early arthritis referral, these slots may be filled from the pool of patients awaiting future consultation.
Prescreening of early arthritis referrals	This may be as simple as review of a 1-page EAC referral sheet (with or without recent laboratory tests and last PCP clinic note) or as extensive as a full chart review with telephone screening. Prescreening must be supplemented by PCP education and transmittal of necessary forms, documents, or records to ensure appropriate decisions about the need for consultation.
Telephone screening	A dedicated phone line (eg, 1-800-EARLYRA [327-5972]) and a trained screener may be an effective way of ensuring the success of regional or system-wide programs. This model facilitates access; ensures transfer of necessary documents and insurance certification; and verifies the referral complaint, symptom duration, and whether referral criteria are met, with the goal of scheduling an early visit.
Public relations programs	All efforts will require program promotion to the targeted health care providers (PCPs, hospital physicians, chiropractors, obstetricians, orthopedists, physical therapists) with frequent and regular reminders.
Internet screening algorithms	Several EACs have an Internet presence; however, these tend to be informational or promotional. Nonetheless, it is possible to develop online screening programs that allow patients to assess whether they may have early inflammatory arthritis, RA, or other common rheumatologic conditions.

What can rheumatologists do to encourage early referral? Not all clinicians or practices have the time or resources to establish a regularly scheduled EAC. Alternatively, a variety of scheduling or intake modifications may be considered. Several models have been used to facilitate the initial evaluation of patients with early arthritis (Table 6). Although each rheumatologist or practice has the potential to facilitate early referral, the challenge is to find a model that works best within each practice or group. Regardless of the model chosen, the goal should be rapid consultation (ie, within 2 weeks) and a process that makes PCP participation and compliance easy.

Referral rules that can enrich rheumatology practices for early RA are summarized in Table 7.<sup>36</sup>

**Table 7. Referral Criteria for Early RA**

- $\geq 3$  symptomatic joints
- $> 12$  weeks of joint symptoms
  - 6–12 wk RA diagnosis recommended
  - Joint symptoms of  $< 6$  mo is better than symptoms of  $< 12$  mo or  $< 24$  mo as entry/referral criterion
- Symmetric arthritis
- +RF or +CCP antibodies
- Hand joint involvement
- Elevated ESR or CRP
- Synovitis of hands on MRI or ultrasound



## Summary

Rheumatoid arthritis may cause severe disability. Prompt treatment with DMARDs ameliorates clinical symptoms and delays disease progression. The goals for therapy are the earliest possible identification of the disease, with referral to the rheumatologist, followed by the use and adjustment of appropriate therapy. The goal for therapy is now remission. Novel treatment strategies and therapeutic agents allow us to aim for remission rather than improvement of disease activity.

Patients who are refractory to methotrexate (or other DMARDs) and those who are at high risk for radiographic damage are candidates for combination DMARDs and/or TNF-blocking therapies (adalimumab, etanercept, infliximab). In clinical practice, initial treatments should be chosen according to the degree of disease activity at baseline and adapted according to a step-up strategy. A more elegant therapeutic approach would be to choose the most appropriate treatment based on the prognosis of RA. Early referral of patients can be facilitated by simple and more complex measures but involves reaching out to PCPs.

## Case Study

A 36-year-old white female is referred to your office for evaluation of pain and positive blood tests.

**History of present illness:** This patient began having symptoms of pain and stiffness in her hands and wrists a few weeks after the birth of her second child 6 months previously. Originally, the pain and stiffness affected just a few of her fingers, but within a few weeks, her hands and wrists were significantly involved. She began noticing difficulty changing diapers in the mornings but felt better as the day went along. These symptoms progressed, and after a few months, she was having severe difficulty preparing baby bottles and getting her 2 children dressed in the mornings. She was severely fatigued to the point of taking frequent naps with her newborn and having to put her 3-year-old child in day care in the afternoons. She attributed her fatigue to having a second child but did not recall this extreme level of fatigue after her first child.

At her baby's next appointment, she brought up these symptoms with the family physician. The doctor examined her hands, squeezing across the first row of knuckles in her hands and feet. This process elicited a significant amount of pain. Further, the doctor commented that the wrists and joints of the hands appeared swollen. The doctor recommended that she have a blood test performed (an "arthritis panel") and take OTC ibuprofen as needed. The patient had given up

nursing her child after a few months and was eager to do something to ease the pain.

She immediately noticed some relief in her symptoms with the ibuprofen but continued to have a significant amount of swelling and stiffness in her hands and wrists. Further, it was now beginning to be uncomfortable walking in the mornings due to pain in her toes and the balls of her feet. Her physician called a few days later to report that some of the blood work was abnormal, so he referred her to an arthritis specialist. After she inquired about the specifics of the blood work, the physician sent her the report below.

Lab Results	
White blood cell (WBC)	5.3 x 10 <sup>6</sup> /μL
Hemoglobin (Hgb)	10.6 g/dL
Hematocrit (Hct)	32.0%
Platelets (Plts)	492.0 x 10 <sup>3</sup> /μL
ESR	67 mm/h
CRP	4.2 mg/dL
RF	360 IU (normal < 14 IU)
Antinuclear antibodies (ANA)	1:80 speckled
Uric acid	4.2 mg/dL
Antistreptolysin O titer	Negative
HLA B27	Negative
Lyme titer	Negative

The next available new patient rheumatology appointment was 2 months away, and the patient was content with continuing the ibuprofen.

After a few months, the patient was seen by a rheumatologist. She continued to have significant pain, stiffness, and swelling in her hands, wrists, and feet. She had significant morning stiffness (> 2 hours). On examination, she had synovitis present in her 2nd and 4th MCPs bilaterally, 1st and 3rd proximal interphalangeal joints (PIPs) bilaterally, and bilateral wrists. Joint exam revealed a tender joint count (TJC) of 17 and a swollen joint count (SJC) of 16 (out of a possible total of 28 joints). Her ability to make a clenched fist was significantly diminished as was her grip strength. She had tenderness with squeezing across her MTPs and probable synovitis in several of her toes. A DAS of 28 joints (DAS28) score calculated in the office was 7.67 (ESR was done in the office at time of visit; see below).

After discussing the diagnosis of RA with the patient (and reassuring her that the low titer ANA result was not meaningful), her rheumatologist recommended further testing including blood work, joint and chest radiographs, administering a purified protein derivative (PPD) to check for tuberculosis, immunization with a pneumococcal



vaccine, and updating other routine adult immunizations. Additionally, it was recommended that she initiate prednisone at 5 mg/d and methotrexate at 15 mg/wk plus folic acid 1mg/d and that she return in 4 weeks to discuss the results of her tests and determine further management plans.

She completed the blood work and testing below.

#### Lab and Other Test Results

Chest radiograph	No abnormalities
PPD	Negative at 2 mm of erythema and induration
Anti-CCP	157 units (strong positive)
Alanine aminotransferase	32 U/L
Aspartate transaminase	23 U/L
Creatinine	0.7
WBC	5.7 k/ $\mu$ L
Hgb	10.1 g/dL
Hct	31%
Plts	523 x 10 <sup>3</sup> / $\mu$ L
ESR	78 mm/h
CRP	5.2 mg/dL
Hepatitis C	No antibody
Hepatitis B	Antibody positive/antigen negative

Joint x-rays revealed diffuse periarticular osteopenia of the hands and feet and small marginal erosions on the head of the right ulnar styloid and bilateral 2nd MCPs.

After 4 weeks, she returned feeling significantly improved. Her fatigue was remarkably better. Her pain and stiffness were greatly reduced. She quantified her morning stiffness at 45 minutes. She was tolerating all of her medications but had concerns about the toxicity of steroids.

On examination, she had 14 TJC and 6 SJC on a 28-joint exam. Her in-office ESR was 48 mm/h resulting in a DAS28 score of 6.09. As her DAS28 still showed she had severe disease, it was recommended that she increase the methotrexate to 20 mg/wk and that she return in 2 months for a decision about escalation of treatment. She was given a pamphlet about the use of biologic agents for RA.

Safety laboratory tests done at this visit revealed normal complete blood count and normal renal and liver function.

Two months later, she returned feeling about the same. She had 9 TJC and 4 SJC on a 28-joint exam, and ESR was 32 mm/h. DAS28 was 5.2.

A decision was made to initiate a TNF inhibitor as she still had severe disease as determined by her DAS28. After discussion of the risks and benefits, the patient was agreeable.

She returned 2 months later for a check-up. She had essentially no morning stiffness. Her 28-joint count showed 2 TJC and 0 SJC, and her ESR was 12 mm/h (DAS28 was 2.89—low disease activity). She was tolerating her medications well and was very thankful for getting back to near normal.

## Commentary: Dr. Cush

This is a typical case of early-onset RA, with the gradual onset of an additive arthritis in typically involved joints (PIPs, MCPs, wrists, etc). Often patients will wait for both persistence of symptoms and/or the addition of new joints before consulting a physician. In this case, the patient waited 6 months before seeking attention. At that point, her PCP was appropriate in his initial approach, but he should have referred her to a rheumatologist at the first sign of a persistent inflammatory polyarthritis, as laboratory results would not change the need for an accurate and expedient diagnosis and plan. The 2-month wait for a rheumatology consultation may have been avoided if the PCP knew how and when to refer this patient to his colleague, the rheumatologist. Hence, the responsibility of facilitating referral rests with the rheumatologist who must promote the need to see such patients in an expedited manner.

The initial evaluation of this patient included far too many expensive and poorly specific investigations. This patient's history and findings exclude any possibility of gout, Lyme disease, lupus, rheumatic fever, or a spondyloarthropathy. An early and accurate diagnosis with the appropriate amount of diagnostic and prognostic testing would have been easily accomplished by coordinated care with the rheumatologist.

By the time this patient saw a rheumatologist and started on methotrexate, she had symptoms of RA for nearly 8 months. She did not achieve the full dose of methotrexate for 10 months and was not begun on a TNF inhibitor until the 11th month—even though she had several indicators of high-risk (aggressive) RA from the outset: polyarthritis, persistent elevation of the ESR and CRP, seropositivity (RF and anti-CCP positivity), very high DAS, and radiographic erosions. If this patient had sought care earlier and if the PCP knew of the medical urgency at hand, this patient could have been taking methotrexate within 3 months of symptom onset and could have been evaluated for additional DMARD or TNF inhibitor therapy by the fifth month (a full 6 months earlier than what was done). Although seemingly minor, many studies have shown that small delays in DMARD or TNF inhibitor use may lead to significant lifelong, radiographic damage.



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