Evidence Supporting the Benefit of Early Intervention in Rheumatoid Arthritis

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ABSTRACT. Numerous challenges confront the rheumatologist in identifying the earliest possible time during which the patient will have persistent rheumatoid arthritis (RA) or risk factors for severe RA. The first challenge is that of accurate diagnosis: clinical assessments are nonspecific and current diagnostic criteria lack sensitivity. Further compounding the problem, the patient may not seek medical attention, or may not be referred to a rheumatologist, until symptoms have been present for some time. Studies indicate that initiating treatment with disease modifying antirheumatic drugs (DMARD) as soon as possible after diagnosis produces significant clinical and functional benefit and appears to retard the rate of radiographic progression of erosions. Delaying treatment by as little as 8 or 9 months sets the stage for damage that cannot be reversed. (J Rheumatol 2002;29 Suppl 66:3–8)

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INTRODUCTION

As our understanding of rheumatoid arthritis (RA) increases, so does our appreciation of its destructive effect on the lives of persons with RA and their families. By no standard can RA be considered a benign disease. While some patients recover spontaneously, most do not; indeed, most sustain significant joint inflammation and erosive damage within the first 2 years of illness[1,2]. Early diagnosis is daunting, since medical attention may be delayed or inappropriate, clinical symptoms are a subjective variable that do not necessarily equate with true extent of disease, serologic markers often lack adequate sensitivity and specificity, and radiographic evidence of joint damage may not appear until disease is fairly advanced.

On the positive side, speedy and aggressive intervention can measurably improve outcome for patients with RA. In particular, early treatment with disease modifying antirheumatic drugs (DMARD) can reverse morbidity, as measured by disability and radiographic progression of joint damage[3,4]. Biologic agents are targeted new therapies demonstrating benefit in patients with suboptimal response to DMARD therapy. Their role in early RA will be closely monitored as the benefits of immediate intervention become better characterized in patients with early RA.

In this article, the obstacles and challenges that befall accurate and timely diagnosis of RA are reviewed along with literature documenting the clinical repercussions of early and delayed use of DMARD.

THE FIRST CHALLENGE: EARLY DIAGNOSIS

Kim and Weisman, in a review of the literature, identified several challenges to early and effective intervention in RA[5]. Among these are lack of definitive criteria, delays in medical attention, and difficulties identifying who is likely to have persistent RA or risk factors for severe disease.

Problems with clinical criteria. One obstacle to early diagnosis of RA is that clinical assessments are nonspecific and current diagnostic criteria lack sensitivity. In their review, Kim and Weisman[5] compared the 1958 and 1987 classification criteria for RA introduced by the American College of Rheumatology (ACR). Because both sets of criteria were based on patients with established disease, they might not be as applicable for patients with early signs and symptoms or relatively atypical features of RA. When the 1987 ACR criteria were used to evaluate patients who had been ill for less than one year, sensitivity was decreased to 81%, compared with an overall sensitivity of 91% observed in patients with more prolonged disease[6].

Dugowson and colleagues[7] compared the 1958 and 1987 ACR criteria with clinician assessments in patients who had RA for less than 3.5 months. Although all patients met the 1958 criteria for probable, definite, or classic RA, only 74% met the 1987 criteria. None of the women with probable RA according to the 1958 criteria met the 1987 criteria. The investigators concluded that the category of probable RA could include persons without RA, and that the 1987 criteria are perhaps more specific but less sensitive.

In a larger study, Harrison and colleagues[8] evaluated patients who had been experiencing early inflammatory

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polyarthritis (swelling in 2 or more joints for at least 4 weeks) for an average of 5 months. At baseline, 38% of the 486 patients met the 1987 ACR criteria by list format, compared with 68% by tree format. Of the hospital-referred patients seen by a physician, 50% were clinically diagnosed with RA. The 1987 ACR criteria could not discriminate between patients who had a physician-based diagnosis of RA and those with other diagnoses and were poor at targeting patients who would develop persistent, disabling, or erosive disease.

Delayed intervention. Patients may not seek medical attention at an early stage of disease. In studies by Chan and associates[9] and van der Horst-Bruinsma and colleagues[10], patients with asymmetric or unilateral joint symptoms tended to seek attention earlier than those with symmetric arthritis or more gradual symptom onset. Patients who presented more acutely (symptom onset within a week) were seen by a specialist sooner.

The Chan study also looked at medical delay in 81 patients with newly diagnosed RA who had access to specialty care[9]. The diagnosis of RA was postponed by a mean of 18 months, primarily because of physician (generalist and rheumatologist) factors. Among patients with symmetric joint involvement and rheumatoid factor (RF) positivity, only 20% were diagnosed as having RA within 2 months. On average, it took 8 weeks for a specialist to see these patients.

Van der Horst-Bruinsma and colleagues[10] evaluated European patients who either presented to a specialized early arthritis clinic (EAC) or were seen at a regular rheumatology clinic. The rheumatologists were able to diagnose RA by the second week of followup, and the diagnosis held throughout the year. Time between symptom onset and first rheumatologist evaluation was 3 months shorter at the EAC compared with the regular clinic. This suggests that early diagnosis is possible, particularly at an EAC, and early referral to a specialist by an astute primary care physician facilitates early diagnosis of RA.

Identifying candidates for early treatment. One of the biggest challenges in managing RA is how to accurately identify (before joint damage has occurred) patients who have either persistent RA or risk factors for severe RA, particularly as more immediate and aggressive disease modifying antirheumatic drug (DMARD) intervention could be particularly rewarding for this population[5].

Kim and Weisman[5] examined these issues within the context of data obtained from population- and EAC-based studies. In evaluating factors responsible for persistent disease, the most important difference between population and EAC studies was the incidence of persistent disease: 27% to 28% for population-based studies[11,12] versus 45% to 94% for most of the EAC-based studies (differences in patient selection criteria could have accounted for this discrepancy)[13-19]. Data from the EAC studies revealed some markers for disease persistence in patients with early RA (Table 1).

Severity of RA is usually measured according to functional disability and radiographic erosions. Kim and Weisman's review noted several predictors of disease severity, including presence of serologic markers of disease activity, large joint involvement, and upper extremity disease (Table 2)[19-21].

Studies examining RF in conjunction with known MHC class II association and defective sulfoxidation show that patients with 2 or 3 of these risk factors have a significant increase in the risk of destructive radiologic findings, compared with patients having none or 1 of these risk factors[22]. Other studies examining only RF and MHC class II disease-associated epitope show that it is possible to predict, with 90% specificity, which patients will have destructive disease by one year. This allows patients with a poor prognosis to be selected for aggressive treatment before they develop overt clinical evidence of RA.

My colleagues and I have been using dual energy x-ray absorption (DEXA) of the hands to assess patients with RA who have active synovitis of the small hand joints but no elevation in acute phase response. These patients have the same risk for disabilities as those with acute phase reactants,

Table 1. Markers for disease persistence in early RA. From Kim J, Weisman M, with permission[5].

Female sex
Relatively high joint count
RF positivity*
ESR > 30 mm/h
Fulfillment of ACR 1987 diagnostic criteria (88% sensitivity, 73% specificity)
Disease activity score ≥ 1.6

*Other serologic markers, including antikeratin antibody, antiperinuclear factor, anti-Sa antibody, and anti-RA33 antibody, measured alone or in complement with RF, may be of significant diagnostic value in RA, but issues of standardization, cost, and availability currently prohibit their clinical use.

Table 2. Risk factors for disease severity†. From Kim J, Weisman M, with permission[5].

Female sex
Large joint involvement
Relatively high joint counts
Upper extremity involvement
Elevation in ESR, CRP level
RF positivity*

*Other serologic markers, including antikeratin antibody, antiperinuclear factor, anti-Sa antibody, and anti-RA33 antibody, measured alone or in complement with RF, may be of significant diagnostic value in RA, but issues of standardization, cost, and availability currently prohibit their clinical use. †In some studies, HAQ scores at baseline correlated with future functional disability[20]. Some studies found a correlation between shared epitope alleles and radiographic erosions[19,21].

but do not yet have the clinical markers that commonly signal the need for treatment[23]. We have found hand DEXA measurement to be reproducible and highly sensitive, allowing changes to be detected over as little as 3 months[24]. In our clinic hand DEXA is now used to monitor deterioration in patients with a slow onset of disease, in whom treatment might otherwise be delayed. This is used alongside other sensitive imaging modalities including magnetic resonance imaging and high resolution ultrasound that can detect the characteristic bone erosions of RA very early.

RATIONALE FOR EARLY TREATMENT

Progressive nature of RA. RA progresses in a manner similar, in many ways, to a malignancy, spreading from one joint to another with local invasion (flare). If we as rheumatologists take the approach developed by oncologists, of treating aggressively and earlier in the disease, there would be a better chance of success for inducing remission and improving longterm outcome.

The early phase of disease represents a unique window of opportunity for intervention. There is evidence that inflammation predominates in this phase of the disease. It is possible that immune mechanisms involved in the pathogenesis may be more responsive to treatment at this time[25].

Inflammation responds to treatment, independent of the duration of the disease. However, the final functional outcome is determined by the duration of symptoms before initiation of therapy. Early treatment is important in the preservation of function for the long term (Figure 1).

Untreated RA is catabolic. Why is early, aggressive intervention so important for patients with RA? It is well documented that the morbidity and mortality of RA approaches that of malignancy[23]. Therefore, it seems logical that early intervention might prevent, ameliorate, or forestall some of the more serious aspects of disease — osteoporosis leading to fatal fracture, for example.

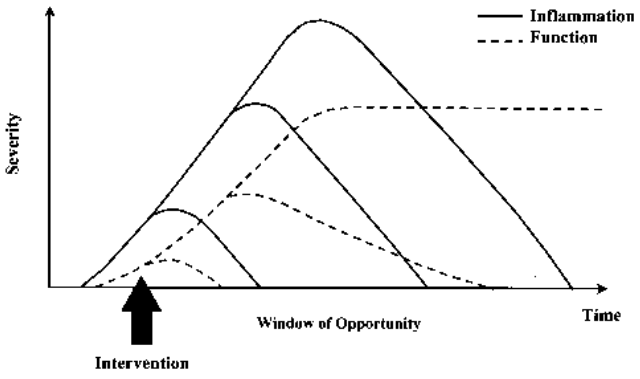

Figure 1. Effect of RA disease duration on inflammation and function. The longer inflammation continues, the greater the degree of functional disability. Intervening early with an appropriately aggressive DMARD controls early inflammation and improves function. Adapted from Ahmed K, Emery P, with permission[25].

Osteoporosis is well recognized in RA, and its assessment has potential as an objective outcome measure. Studies of bone mass (via DEXA) scans in patients with RA of more than 6 months showed loss of bone mass, compared with persons who had RA for a shorter time. Patients with active disease (measured by elevation in C-reactive protein, CRP) continued to lose a significant amount of bone mass. When active disease was controlled within the first 2 years of illness, bone loss subsided[26,27].

Using bone density as an outcome measure also makes it possible to assess the effect of treatment with corticosteroids. Over the first year, patients treated with the highest mean dose of corticosteroids (> 5 mg/day prednisolone) lost less bone than those treated with a lower dose (1–5 mg/day prednisolone). These data confirm that untreated, active RA leads to catabolic consequences.

Established functional deterioration tends to be permanent. Another strong argument in favor of early treatment is that radiographic evidence of damage often appears within the first 2 years of disease. Once erosions develop, they cannot be reversed.

The presence of radiographically observed joint damage does not necessarily correlate with clinical symptoms and functional capability. Evidence from an early arthritis clinic in Birmingham, England, indicates that patients are symptomatically at their worst when they present, and that symptoms improve over time[28]. This contrasts with functional grade, which stabilizes but does not improve in the 3 years after the patient presents.

The longer RA goes untreated, the more difficult it becomes to control inflammation and improve function[29]. If we want to restore our patients to normality, we must do that in a relatively early stage, before significant damage has occurred.

EARLY INTERVENTION WITH DMARD

Several key studies from the literature strongly support the benefit of early drug therapy for improving clinical outcome and ameliorating radiographic progression in patients with RA. DMARD appear to offer more advantage than drugs that do not modify the course of disease.

Improved clinical outcome. Van der Heide and colleagues[30] completed a study in which 238 patients who had RA for less than one year were randomized to receive either a DMARD or a nonsteroidal antiinflammatory drug. The primary study endpoints were functional disability, pain, joint score, and erythrocyte sedimentation rate (ESR) at 6 and 12 months, as well as progression of radiographic abnormalities at 12 months. Patients were assessed every 3 months.

At the end of 12 months, patients who had received DMARD experienced clinically important improvement in disability, pain, joint score, and ESR (Table 3), compared with patients in whom DMARD were postponed. DMARD

Table 3. Changes from baseline in DMARD and NSAID groups at 12 months*. From van der Heide A, *et al*, with permission[29].

Primary Endpoint	NSAID Group (n = 57)†	DMARD Group (n = 81)†	Difference‡
Disability score	–0.1	–0.4	0.3
Pain score, mm	–11	–21	10
Joint score	–50	–89	39
ESR mm/h	–5	–16	11
Radiologic damage score§	+8	+7	1

* Ranges for endpoint variables are as follows: disability score, 0 to 3; pain score, 0 to 100 mm; joint score, 0 to 534; ESR, 1 to 140 mm/h; radiologic damage score, 0 to 448. † Values are the mean (–SD, +SD). Negative values indicate improvement for all endpoints. ‡ Values are the mean difference (95% CI); difference was calculated by subtracting the DMARD from the NSAID value. § Numbers of patients tested were 43 in the NSAID group and 128 in the DMARD group.

treatment also produced improvement at 6 months. Radiographic abnormalities progressed in both groups, but were worse in the non-DMARD group. The investigators concluded that immediate introduction of DMARD may produce the most effective results in patients with early RA.

Delayed radiographic progression. Stenger and associates[31] compared the effects of aggressive treatment with that of stepped care on radiographic progression of RA in 228 patients who had been diagnosed for less than one year. The aggressive treatment regimen consisted of DMARD (sulfasalazine, methotrexate), initiated immediately after diagnosis and adjusted according to levels of CRP.

Patients in the treatment group were assigned to a "high risk" (HR) or "low risk" (LR) group at study entry. Control (stepped care) patients were assigned to a HR or LR subgroup retrospectively, at 2 years of followup. All study participants were evaluated monthly for swollen joint count, Ritchie articular index, grip strength, duration of morning stiffness, and CRP. Hand and foot radiographs were obtained every 6 months, and joint damage was assessed according to van der Heijde's modified Sharp score. Absolute radiographic progression of disease was measured after 2 years of followup (median progression was 20 Sharp-score points; slow and fast progression was less or at least 20 points, respectively).

In the 2 year followup (Table 4) in patients treated aggressively (DMARD initiated immediately after diagnosis) radiographic progression was significantly lower than in the control group. Based on this study[31], the rate of radiographic progression can be reduced in patients with RA, provided that treatment is initiated immediately with fast-acting DMARD and that the dosage and/or drug regimen is monitored closely and adjusted rapidly in the case of insufficient response.

DELAYED TREATMENT WITH DMARD

How late is too late? The first 2 years of RA appears to be a critical time, during which treatment with DMARD produces significant improvement that appears to be sustained later in disease. Delaying treatment beyond this therapeutic window can lead to irreparable damage and functional disability.

Determining when patients with RA are most responsive to treatment was the subject of a 2 year, double blind, placebo controlled trial conducted by Borg and colleagues[32]. All 137 study participants had RA for less than 2 years. "Early" treatment (as soon as possible after diagnosis) with auranofin was compared with DMARD treatment that was started after clinical deterioration was evident (about an 8 month delay). By the end of the second year, early treatment

Table 4. Effect of early DMARD treatment on radiographic progression of RA (intention to treat analysis). From Stenger AAME, *et al*, with permission[30].

Time (mo)	Treatment HR (n = 8)	Control HR (n = 42)	p*	Treatment LR (n = 61)	Control LR (n = 47)	p†
6	8.0	8.5	0.45	3.0	1.0	0.04
12	15.0	17.5	0.22	6.0	3.0	0.08
18	19.5	26.5	0.07	7.0	7.0	0.37
24	26.0	35.0	0.03	11.0	8.0	0.36

* One sided.
† Two sided.
HR: high risk; LR: low risk.

had produced significantly greater improvement in physical function than delayed treatment.

In a subsequent study, Egsmose and colleagues[33] followed 75 of these patients for an additional 3 years. At 5 years, the early treatment group had significant improvement in Ritchie index, number of swollen joints, duration of morning stiffness, grip strength, and general health. The delayed treatment group showed improvement in only the Ritchie index and duration of morning stiffness. The early group also experienced significant improvement in all outcome variables: pain, Health Assessment Questionnaire, Keitel functional index, and Beck depression scale. In the delayed group, only pain improved significantly.

The results of radiographic assessment also supported the benefit of early treatment. While the total number of erosions and the Larsen score increased in both treatment groups, the early treatment group fared better than the delayed group after one year — an advantage that was maintained throughout the study. At 5 years, the Larsen score and the erosion score in the delayed group had reached values roughly twice those in the early group. This significant difference remained after 5 years. The same pattern was observed in number of involved joints and number of eroded joints, in favor of the early treatment group. Thus, progression of radiographic joint destruction was slowed in the early treatment group, producing a 100% difference in radiographic scores at 5 years.

The investigators speculate that the optimal time to intervene in RA may be before the formation of pannus, which leads to irreversible erosions. This may explain why treatment started early produces sustained benefits. It may also account for the failure of any drugs to do more than retard the progression of erosions. These findings underscore the importance of starting DMARD therapy as soon as the diagnosis of RA has been confirmed.

Consequences are prolonged. Tsakonas and colleagues[34] also assessed the longterm effect of delaying DMARD in patients with early RA (duration of 9 mo). In their study, 119 patients who participated in a 9 month, placebo controlled randomized trial of hydroxychloroquine sulfate (HCQ) were followed prospectively for 3 more years. Patients randomized to HCQ constituted the early treatment group, while those who received placebo were considered as the delayed treatment group. Each year, patients were evaluated for pain [Arthritis Impact Measurement Scale (AIMS), Stanford HAQ, physical disability (AIMS and HAQ), and RA global well-being (AIMS)]. Of the original patient cohort, partial data were available on 115 (97%) and complete data on 104 (87%).

Over the 3 years of study, pain and physical disability outcomes remained worse for the delayed versus the early treatment group. These findings support those of Egsmose[33], and again show that even a relatively short delay in starting DMARD has a significant effect on longterm outcome for patients with RA.

CLINICAL GUIDELINES FOR EARLY REFERRAL

As clinical evidence strongly supports the observations that structural damage occurs early and permanently in RA and intervention slows the progression of damage, a rapid referral to a rheumatologist is recommended when RA is suspected.

To expedite this process a referral recommendation was developed to serve as a clinical guide for primary care physicians[35]. The consensus is that the presence of any of the following be the criteria for referral to a rheumatologist:

- ≥ 3 swollen joints
- metatarsophalangeal/metacarpophalangeal involvement
- morning stiffness ≥ 30 min

SUMMARY

In patients with RA, uncontrolled inflammation causes damage that may not be reversible. Early suppression of this inflammation can potentially avoid, or at least retard, the progression of joint damage. There appears to be a therapeutic window, occurring within the first 2 years of RA, when patients are most likely to sustain maximum benefit from receiving DMARD. This window may be the interval between symptom onset and the formation of pannus. Giving DMARD during this early time produces clinical, functional, and radiographic benefits that are sustained throughout at least 5 years of followup. Similarly, delaying DMARD therapy for as little as 8 or 9 months after initial diagnosis appears to directly contribute to functional and radiographic deterioration in patients with RA.

These findings are a "wake up call" to all physicians who encounter patients with RA in their daily practice. It is incumbent upon primary care and other gatekeeper physicians to know when to suspect RA and to arrange prompt referral to a specialist at the earliest suggestion of disease. Specialists, in turn, must initiate the appropriate diagnostic tests and implement therapy with DMARD as soon as the diagnosis has been confirmed. Given the longterm devastating consequences of RA, it is incumbent on those who suspect RA to seek immediate diagnosis and treatment in the therapeutic window before irreversible damage occurs.

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