Early Rheumatoid Arthritis — Is There a Window of Opportunity?

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ABSTRACT. The early diagnosis and treatment of nascent rheumatoid arthritis (RA) has become a prime objective for rheumatologists and clinicians who care for patients with arthritis. Population-based studies have consistently shown that patients with RA are at substantial risk for progressive joint damage, disability, and increased morbidity and mortality. These inevitable outcomes are closely linked to the consequences of rheumatoid inflammation, which begins early and is progressive in all. At issue is whether early diagnosis, coupled with aggressive therapy, might alter the natural history of this RA. If this "window of opportunity" exists, then outcomes should be substantially altered by delivering the right therapies at the right time. A growing body of evidence has emphasized the consistent clinical and radiographic benefits of early, aggressive treatment of RA. These studies confirm that all therapies — monotherapy, combination disease modifying antirheumatic drugs (DMARD), biologics — work better in early disease than in long-established RA. Earlier identification, referral, and an accurate diagnosis of RA can now be rewarded with highly effective DMARD or biologic therapies. Rheumatologists should rise to the challenge and educate clinicians about this window of opportunity, the potential for remission, and superior clinical responses when patients with early RA or undifferentiated arthritis are referred to and managed by experts in aggressive rheumatologic care. (J Rheumatol 2007;34 Suppl 80:1-7)

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EARLY DIAGNOSIS UNDIFFERENTIATED ARTHRITIS RHEUMATOID ARTHRITIS
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INTRODUCTION

The early diagnosis and treatment of nascent rheumatoid arthritis (RA) has become a prime objective for rheumatologists and clinicians who care for patients with arthritis. A growing body of evidence has emphasized the consistent clinical and radiographic benefits of early, aggressive treatment of RA and the unfortunate consequences of either delayed or ineffective therapies[1,2].

Early diagnosis of any disease is a challenge to all physicians and healthcare systems. This tenet has been fundamental to advances in the management of neoplastic, infectious, neurologic, developmental, and autoimmune disorders. In each of these, early recognition and treatment increases the odds of optimal outcomes.

Population-based studies have consistently shown that patients with RA are at substantial risk for progressive joint damage, disability, and increased morbidity and mortality. These inevitable outcomes are closely linked to the consequences of rheumatoid inflammation, which begins early and is progressive in all. At issue is whether early diagnosis, coupled with aggressive therapy, might alter the natural history of this destructive and dreadful disease. If in fact this "window of opportunity" exists, then outcomes should be substantially altered by delivering the right therapies at the right time.

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What Is Early RA?

While most rheumatologists believe "the earlier, the better," there is no formal definition of "early RA." In randomized clinical trials, patients with "early RA" were included if they had a diagnosis of RA for less than 3 years. Calculating the duration of disease may also prove problematic, as patient recall or documentation of symptom onset, physician diagnosis, or abnormal serologies varies considerably[3]. When Aletaha and colleagues surveyed rheumatologists from Europe and the USA, they found that the majority defined "early RA" as symptom duration < 3 months[4].

Population-based incidence rates for RA have been studied extensively. In 1994, it was estimated there were nearly 170,000 new cases of RA in the United States[5]. The incidence of RA varies within different populations and communities. Thus, in developed countries the incidence rate of early RA varies between 5 and 45 cases per 100,000 patients per year (patient-years)[6,7]. If one conservatively estimates the incidence of RA in North America to be 20 cases per 100,000 patient-years, then we might anticipate nearly 75,000 new patients with RA in the USA and 7,500 in Canada in the next 12 months.

However, this would be only a subset of all patients who present with new-onset polyarthritis, as an equal or greater number of patients will manifest an undifferentiated inflammatory polyarthritis at the outset.

In many early arthritis clinics in Western Europe the frequency of undifferentiated arthritis (UA) exceeds that of RA[8,9] and may account for up to 50% of all new patients with inflammatory arthritis. In a report from the Leiden early arthritis clinic it is estimated that, of all patients with UA, 30% remit, 30% develop into RA [based on American College of Rheumatology (ACR) criteria], and up to 20% remain undifferentiated[9]. Despite the prevalence of UA and an uncertain progression to RA, many rheumatologists are capable of diagnosing RA at the first encounter. When rheumatologists in an early arthritis clinic were asked to diagnose the arthropathy, those diagnosed with definite or probable RA in the first 2 weeks were > 80% likely to retain their original diagnosis[10]. Patients designated as having UA (not meeting ACR classification criteria) from the outset will require close observation and time to identify their subsequent course — remission or progression to RA or other arthropathy. A recent analysis of UA cohorts revealed those factors with the greatest predictive diagnostic value in determining RA progression[11]. From these studies, clinicians can be assured that their clinical acumen and attention to typical RA features (e.g., pattern of joint involvement, symmetry, severity of morning stiffness, number of joints, acute-phase reactant elevation, and seropositivity) can reliably predict and identify those patients at risk for developing early RA[11].

Is There a Window of Opportunity?

Advocates for a therapeutic window of opportunity believe that disease modification can be optimized by applying the right intervention at the right time. If true, the chronology and type of intervention should greatly influence disease progression. Thus, treatment within this timeframe would yield optimal outcomes such as true remission, therapeutic remission, or a halting of disease progression as measured by functional or radiographic outcomes.

Proving this hypothesis is challenging and requires the study of a large number of patients with early RA (or undifferentiated inflammatory arthritis) treated with conventional or aggressive therapies over an adequate period of observation. To date, studies examining this concept have been limited to 12 or 24 months' duration and have relied on clinical response or radiographic outcomes. Unfortunately, these outcomes are somewhat imprecise, as patients shown to have the best outcomes [e.g., ACR20 responders, remission on Disease Activity Score (DAS), no radiographic progression] may still have residual inflammatory activity as measured by swollen joint counts, or subclinical synovitis detected by ultrasound or magnetic resonance imaging[12,13].

As mentioned above, our definition of early disease may be imprecise in some. Several reports have identified patients with abnormal serologies (rheumatoid factor-positive, cyclic citrullinated peptide-positive) that antedate the onset of RA by months to years[14]. Investigators have shown that the earliest pathologic lesions in RA are vascular abnormalities that also precede synovial proliferation and clinically manifest disease. We know that newer imaging modalities can show evidence of erosions that antedate radiographic erosions[15]. Hence, for many patients it is likely that rheumatoid inflammation has been present and active for many months before classic symptoms or signs of RA prompt medical attention.

The definition of early RA is therefore arbitrary and depends on access to care, and whether a pathologic, serologic, clinical, or radiographic measure is employed. While rheumatologists use phrases like "the earlier, the better" or "treat now, not later," the cutoff point for early RA ranges widely, generally from 3 to 36 months. One survey defines the patient with early RA as having a disease or symptom duration of less than 3 months[4]. Regulatory randomized controlled trials in early RA, on the other hand, are limited to patients with a disease duration of less than 3 years[16-18].

To establish the "window of opportunity" concept, several lines of evidence are needed. First, prospective, randomized, controlled trials will need to prove that an effective therapy works better when used early. Second, trials are needed to show that "the earlier, the better" is true — meaning that over a range of disease durations, therapies will have to clearly establish a time-dependent optimal response (i.e., remission). Lastly, studies of at-risk populations will need to show intervention and time-dependent prevention or meaningful alteration of RA.

The Earlier, the Better

The recent tumor necrosis factor (TNF) inhibitor trials have consistently shown that early aggressive use of TNF inhibitors led to outcomes that were superior to those observed in patients with established disease. This has been specifically shown in subanalyses of the adalimumab DE019 trial, etanercept TEMPO trial, and the infliximab ATTRACT trial (Table 1)[19-22]. This observation has also been true for traditional DMARD. Anderson and colleagues have revealed that regardless of the DMARD used, clinical responses were consistently better when the DMARD was used earlier in the disease[23].

Lard and colleagues studied RA patients with early disease (mean disease duration 4–5 months) and demonstrated distinctly different outcomes when patients were divided into those given immediate or delayed DMARD therapy[24]. While patients given early DMARD therapy

Table 1. Subanalyses comparing response rates with TNF inhibitors used in patients with early versus established RA.

		Early RA Patients			Overall RA Population (Established + Early Patients)		
Study	Agent	Disease Duration, yrs	N	ACR 20 Responses, %	Disease Duration, yrs	N	ACR 20 Responses, %
DE019[19]	Adalimumab	< 2	55	70	≥ 2	363	62
TEMPO[20,21]	Etanercept	≤ 3	77	77.9		503	75
ATTRACT[22]	Infliximab*	< 3	82	37	> 3	428	42

* 3mg/kg q 8 wks.

(median delay 15 days) had negligible radiographic changes after 2 years, those with a delay in DMARD initiation (median 123 days) demonstrated significant radiographic progression over 2 years (Figure 1A). A 4-year followup study of these same patients showed that between the second and fourth years, the 2 groups progressed equally; however, those with a delay in DMARD initiation had more damage over time[25].

Other DMARD studies have also documented the longterm, downstream benefits of earlier intervention. The "Combinatietherapie Bij Reumatoide Artritis" (COBRA) trial examined the effects of early DMARD intervention in DMARD- and prednisone-naive patients

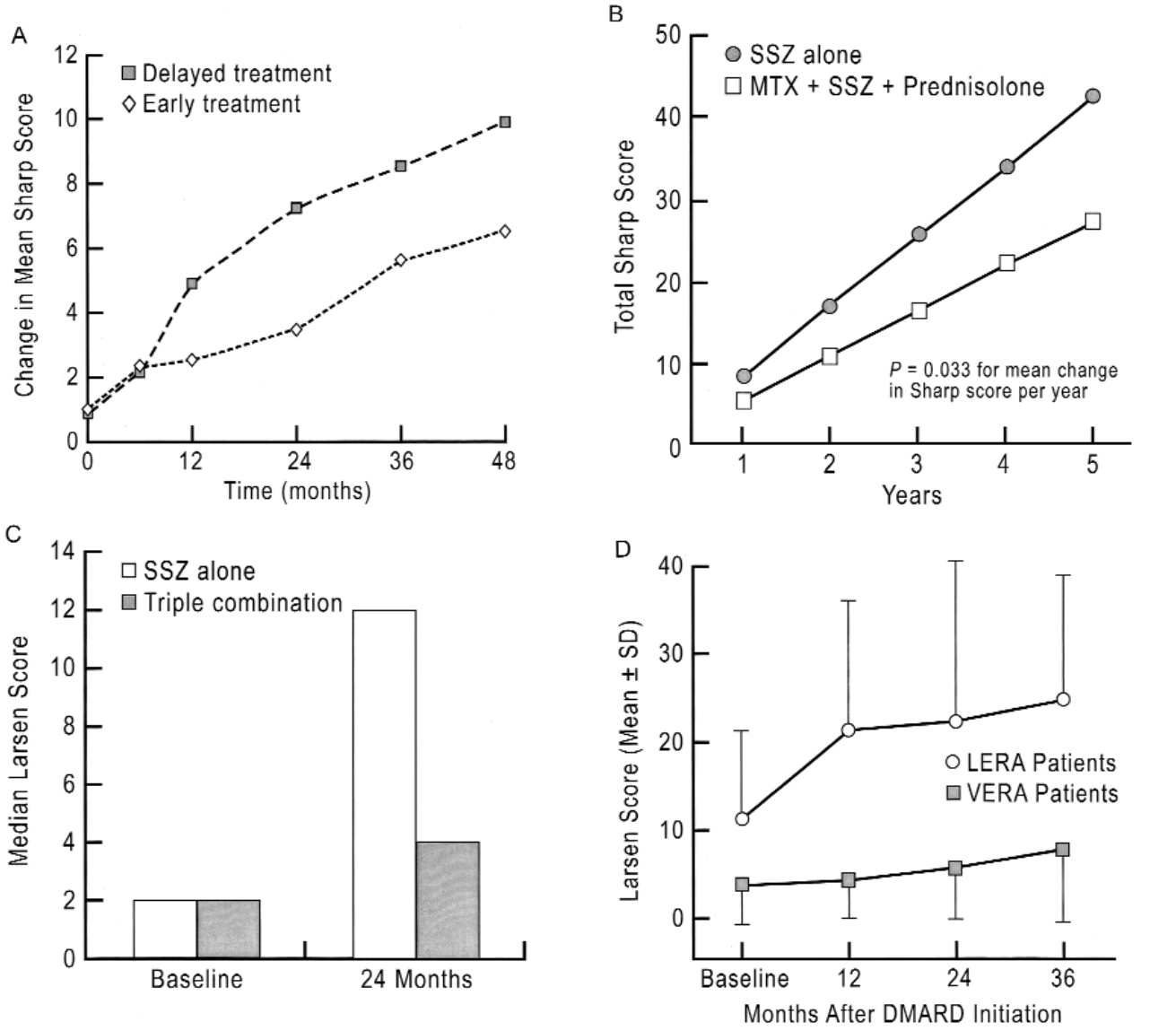

Figure 1. Structural influence of early and aggressive DMARD use in early RA. A. Early DMARD: median 15 days. Delayed treatment: median 123 days[25]. B. p = 0.033 for mean change in Sharp score per year[27]. C. Median duration of disease 6 months[29]. D. VERA: patients presenting within 3 months of symptom onset. LERA: patients presenting within 9 months–3.5 years of onset (median 12 months)[32]. $p < 0.05$. Original sources: A. van Aken J, et al. Ann Rheum Dis 2004;63:274-9; B. Landewé RB, et al. Arthritis Rheum 2002;46:347-56; C. Möttönen T, et al. Arthritis Rheum 2002;46:894-8; D. Nell VP, et al. Rheumatology Oxford 2004;43:906-14. All with permission.

with early RA (mean disease duration 4 months)[26]. Patients treated with 6 months of aggressive combination therapy [sulfasalazine, methotrexate (MTX), and high-dose prednisolone] showed significantly higher ACR20 responses (72% vs 49%), higher remission rate (28% vs 16%), and less radiographic damage and disability in the ensuing 5 years (Figure 1B)[26,27]. Similarly, the 2-year Finnish Rheumatoid Arthritis Combination Therapy (FinRA-Co) trial studied 195 patients with early RA, and showed that early aggressive combination DMARD therapy yielded higher remission rates (38% vs 18%) and less radiographic progression (Figure 1C)[28,29]. Moreover, a subanalysis of those treated with sulfasalazine alone showed that remission was less common for those experiencing a DMARD treatment delay > 4 months compared with those treated promptly (11% vs 35%, respectively)[29]. A recent report showed that even after 11 years of followup, the early, aggressive treatment cohort had significantly more remissions (than monotherapy) and better functional outcomes[30]. Both the COBRA and FinRA-Co studies demonstrated that early, aggressive therapy reduced work disability, premature retirement, and sick leave for those patients with early RA treated with the more aggressive DMARD regimen[31].

Nell and colleagues studied the timing of DMARD initiation by comparing patients with early RA (median disease duration 12 months) to those with very early RA (median disease duration 3 months)[32]. After 36 months of conventional DMARD therapy the very early DMARD-treated group exhibited greater ACR20 (70% vs 40%), ACR70 (55% vs 20%), and DAS improvements (2.8 vs 1.7). Also, the patients with very early RA had significantly less radiographic progression as measured by Larsen scores (Figure 1D).

These studies support the claim that the earlier the treatment, the better the clinical outcome in RA. Moreover, these studies confirm that all therapies — monotherapy, combination DMARD, biologics — work better in early disease than in long-established RA. Such findings support the need for early, aggressive management in RA. Despite many studies documenting the irreversible consequences associated with short-term treatment delays, many clinicians remain reluctant to overtreat patients with mild or nonlimiting early RA.

Can Overtreatment Be Advocated in Early RA?

Physicians are conservative by nature and training. They swear by the principles of Hippocrates to protect the patients' welfare, while avoiding harm. However, the aforementioned benefit of early and aggressive treatment of RA argues against such conservatism. At issue is whether aggressive treatment of early RA may be viewed as overtreatment. Unfortunately, the term "overtreatment" implies a baseless or unwise therapeutic approach. Overtreatment should not be confused with overprescribing, inappropriately prolonging therapy, using expensive drugs, or promoting polypharmacy. I believe the available evidence suggests that overtreatment and aggressive treatment are synonymous and should be advocated in patients with early RA — as such patients are routinely subjected to delays in diagnosis and undertreatment. While concerns for patient safety should always be paramount, experience has shown that serious adverse events (e.g., serious infections) seen with biologic or combination DMARD therapy are less frequent in patients with early disease. This is predictable, as infections and other serious adverse events become more likely with comorbidity, steroid use, and disability.

Aggressive overtreatment of early RA can be advocated based on published reports focusing on the timing of therapy and the "window of opportunity." Hence, the earlier a DMARD, biologic, or combination regimen is used, the better the clinical and radiographic outcomes. Quinn and coworkers investigated this approach in a trial of 20 patients with early RA (≤ 1 year disease duration), all of whom received optimal MTX therapy, while half also randomly received infliximab infusions[33]. At the end of 1 year, patients receiving combination MTX/infliximab therapy had no new erosions and greater ACR70 responses (67% vs 30%). During the second year, 70% of the infliximab induction group maintained these clinical responses with a mean DAS score of 2.05. This study was the first to document the induction potential of TNF inhibition in patients with early RA and to demonstrate that such aggressive and expensive therapy may be withdrawn after a year.

In the BeSt study ("Behandel Strategieën," i.e., Treatment Strategies), patients with early RA were randomized to one of 4 initial treatment strategies: (1) sequential monotherapy; (2) step-up to combination therapy (both starting with MTX); (3) initial combination therapy with MTX, sulfasalazine, and a tapered high dose of prednisone; or (4) initial combination therapy with MTX and infliximab[34-36]. Therapy adjustments occurred at 3-month intervals, and if the DAS was > 2.4, a proscribed change in regimen ensued. In the first year of therapy, the COBRA combination regimen (Group 3) and MTX plus infliximab (Group 4) were superior to the other regimens and required fewer DMARD changes. After the first year, patients in remission were able to withdraw from therapy: over half the patients treated with a biologic (Group 4) were able to discontinue infliximab and maintained their response taking MTX alone. By Year 3, 15% of patients were in remission taking no DMARD. These data again show the clinical value and remission-inducing potential of timely aggressive combination DMARD (or DMARD plus biologic) therapy in high-risk patients with early RA.

As we aim to deliver timely treatment in the patient with incipient RA, the ultimate goal might be to prevent development to RA. Numerous early arthritis clinics have shown that patients with early UA (not achieving diagnostic criteria for RA) usually outnumber RA patients and that only 30%–40% of UA patients develop into RA[8,9]. The Probable Rheumatoid Arthritis Methotrexate Versus Placebo Therapy (PROMPT) trial addresses whether aggressive overtreatment during this "window of opportunity" may avert the onset of RA[37]. This novel 12-month, double-blind placebo-controlled trial randomized 110 patients with UA to receive MTX 15 mg/wk or placebo, and examined the proportion of patients who developed RA after 12 months. At 1 year, MTX treatment was shown to significantly reduce progression to RA and more MTX-treated patients achieved remission and had less radiographic progression. Further analysis of these data interestingly revealed that the benefits of early aggressive MTX treatment were largely observed in patients with antibodies against citrullinated peptides[37].

In summary, these studies demonstrate the potential for disease modification when aggressive therapy is delivered early during rheumatoid inflammation. The use of either combination DMARD or TNF inhibitors in early RA not only affords the patient significant clinical and radiographic benefits, but also offers the potential for real drug-free remission or the realistic goal of reduced biologic or DMARD dependence. This contrasts with established or longstanding RA, where remission is rare and prolonged DMARD dependence is expected. Lastly, demonstration of RA prevention by overtreatment of undifferentiated inflammatory arthritis in the PROMPT trial further supports the concept of a therapeutic window of opportunity.

Changing the RA Treatment Paradigm

Rheumatologists universally support the concept of early diagnosis and aggressive treatment of RA. Yet there remains a chasm in care that has not been addressed by the rheumatologic community. This unmet need includes impediments to expert care, lack of a concerted early RA effort, and educational gaps in the primary care sector with regard to the importance of early diagnosis and treatment.

One of the primary obstacles to early diagnosis is patient access to rheumatologic care. In the USA, there is a large RA population (> 2.2 million), many of whom have not been diagnosed or treated (~700,000). Of the 1.5 million who have been diagnosed, > 800,000 are cared for by primary care physicians (PCP) and roughly 700,000 are cared for by rheumatologists. Whereas rheumatologists usually care for patients with established disease, PCP are more likely to see patients in the first few weeks of their illness, when few joints are affected, laboratory abnormalities may be absent, and radiographs are normal. Rheumatologic consultation would be highly advantageous at this crucial stage of disease when remission and optimal clinical responses are most likely. However, PCP and patients view this as problematic, as there are fewer than 3000 practicing rheumatologists in the USA, and referral wait-times are weeks to months for most rheumatologists.

Access issues must be addressed by the rheumatologic community if rheumatologists are to guide RA care during this window of opportunity. Several measures can be employed to facilitate the referral of patients with new onset disease[1,38]. Foremost among these is promotion of a referral policy with a special focus on new-onset RA or inflammatory arthritis. By communicating the need for and benefits of early referral and rules for referral[6], the rheumatologist will better educate his referral base and create a facilitated access pathway for patients with early inflammatory arthritis. In addition to sending "Dear Colleague" referral letters, other means of facilitating access might include distributing early-arthritis referral forms, forming a dedicated early-arthritis clinic, using physician extenders to screen for early RA, telephone or chart screening measures, or overbooking early-arthritis referrals for rapid assessments (Table 2).

Nevertheless, the longer the wait for referral, the less likely the rheumatologist will see patients with very early RA or UA. Hence, my current practice is to promote and guarantee same-week consultation for patients meeting usual referral rules (i.e., > 6 weeks of joint symptoms, positive metacarpophalangeal or metatarsophalangeal squeeze test, abnormal laboratory results, etc.). While this will undoubtedly increase intake volume, adopting a triage and stratification approach to new patient consultations can improve satisfaction for patients, PCP, and rheumatologists alike.

Earlier identification, referral, and an accurate diagnosis of RA can now be rewarded with highly effective DMARD or biologic therapies. Rheumatologists should rise to the challenge and educate clinicians about this

Table 2. Measures to facilitate early RA referral and access to the rheumatologist.

- Promotion of referral policy
  - "Dear Colleague" referral letters
  - Rules for referral
  - Early arthritis fax referral forms
- Dedicated early arthritis clinic day (e.g., Tuesday is early arthritis day)
- Physician extenders early RA screening clinic
- Telephone or chart screening of referrals
- Overbooking early arthritis referrals for rapid assessments
- Same-week consultation for early RA referrals

window of opportunity, the potential for remission, and superior clinical responses in early disease when patients with early RA or UA are referred to and managed by experts in aggressive rheumatologic care.

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