Editorial

Early Arthritis Clinics: If You Build It Will They Come?

The mantra of "early diagnosis and aggressive treatment" for rheumatoid arthritis (RA) has become a cornerstone belief for most rheumatologists. Although there have been trends showing shorter referral times from primary care physician to rheumatologist and declining lag times in the initiation of disease modifying antirheumatic drug (DMARD) therapies[1-3], a majority of patients with new onset rheumatoid arthritis (RA) still experience significant delays in early diagnosis and optimal care. Causes for delay are multifactorial and include patient reluctance to seek immediate care, diagnostic inaccuracies, over-reliance on laboratory diagnostics, and substantial delays in rheumatology referral[4-6].

Considerable research and clinical effort in the last decade has declared the success of novel diagnostic and therapeutic programs focused on those with early inflammatory arthritis or RA. This body of work has given credence to the possibility that an early RA diagnosis and early aggressive interventions might lead to significant longterm benefits.

In this issue of *The Journal*, Raza and coworkers examine the utility of anti-cyclic citrullinated peptide (CCP) antibodies in patients with very early inflammatory arthritis[7]. Their findings clearly show the practicality and importance of serologic testing for both serum rheumatoid factor (RF) and anti-CCP antibodies in making an accurate diagnosis in those with persistent symptoms of RA. These findings serve as a challenge to the rheumatologist to amend the manner in which early arthritis patients are currently diagnosed and treated.

While all rheumatologists strongly advocate for early diagnosis and aggressive treatment of RA, few have revamped their clinical practice or established "early arthritis clinics" to facilitate such optimal care[8,9]. The time has come for clinicians to reevaluate and consider the advances of the last decade as an impetus to create novel pathways to facilitate diagnosis and treatment for those with early inflammatory arthritis.

WINDOW OF OPPORTUNITY

Over the last several years, the definition of early RA has changed such that surveys now suggest that "early" RA is best described as those with less than 3 months of symptoms and disease activity[10]. Yet despite the narrowing of this definition, very few RA patients are seen within the first 6–12 months of their disease onset.

Clinical trials have also changed over time such that recent early RA trials have included only patients with less than 3 years' disease duration. On average, these patients had a mean disease duration of 0.7–0.9 years[11-13], with few having 3 months or less as optimally suggested by surveys. This focus on earlier and potentially modifiable disease suggests the possibility of a therapeutic window of opportunity. Although not formally defined, such a chronological construct identifies the period of disease onset or course wherein appropriate intervention yields the greatest impact on disease progression. The goal of such targeted intervention would then be true remission, therapeutic remission, or at least a halting of disease progression as measured by functional and radiographic change. The ominous nature of this window of opportunity is supported by data showing early evidence of erosive disease (as early as 4 months) by radiography and more so by magnetic resonance imaging[14,15].

Access to patients within the therapeutic window is strongly dependent upon an early and accurate diagnosis of RA. Research from several early inflammatory arthritis clinics has shown only a minority of patients presenting with inflammatory oligoarthritis or polyarthritis will be ultimately diagnosed as having RA[9,16-18]. This is not surprising, as few patients with early RA will meet American

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College of Rheumatology (ACR) classification criteria for the diagnosis of RA, and less than half will have a positive serologic test for IgM RF[19] during the first 6 months.

Nonetheless, most rheumatologists assert that RA can be easily diagnosed with a timely and accurate clinical assessment and few, if any, laboratory investigations. In one early arthritis clinic, the accuracy of a rheumatologist's early RA diagnosis was confirmed. Early arthritis patients were evaluated after 2 weeks and were later declared to have either definite or probable RA. One year later, over 89% of the definite RA patients retained this diagnosis and only 5% had a change in diagnosis. Of those with probable RA, 72% had definite RA a year later and only 16% had a change in diagnosis[20]. Further, the guidelines established by Emery and others (Table 1) have shown us that patients can be referred for an early evaluation by having: (1) 3 or more swollen joints; (2) involvement of metacarpophalangeal or metatarsophalangeal joints; and (3) morning stiffness greater than 30 minutes[6]. The accuracy of a subsequent early RA diagnosis can be enhanced by finding: (4) chronicity (duration of symptoms longer than 12 weeks); (5) elevated acute phase reactants (erythrocyte sedimentation rate or C-reactive protein), or serologic abnormalities (RF or anti-CCP antibodies). Hence, there are guidelines for high yield referrals and simple measures to ensure the accuracy of an early RA diagnosis.

ROLE OF CCP ANTIBODIES

The emergence of anti-CCP antibody assays as a new serologic marker for RA is a significant advance in rheumatologic care. This assay retains the sensitivity of serum RF while demonstrating far greater specificity (> 95%) for diagnosis of RA[21]. CCP antibodies can be assayed in conjunction with traditional serum RF to complement and supplement the diagnostic intent of such testing; they have been linked with early aggressive RA, a greater risk of erosive disease, greater disease activity, and, possibly, an association with the shared epitopes (e.g., HLA-DRß1 alleles)[21] seen in RA. The importance of anti-CCP antibodies is suggested by their presence months before onset of RA and the augmented ability of citrulline-rich peptides to bind to shared epitopes linked with RA pathogenesis[22,23]. I would suggest that testing for both RF and CCP may yield clinically useful information, especially in those with early inflammatory polyarthritis. Thus, it appears that patients double-positive for RF and CCP are at greater risk for radiographic progression, while double-negative patients may run a more benign course[24].

Table 1. Guidelines for referral to early arthritis clinic. Adapted from Emery P, *et al*[6], *Ann Rheum Dis* 2002;61:290-7 and from Kim JM, Weisman MH, *Arthritis Rheum* 2000;43:473–84.

Guidelines
- ≥ 3 swollen joints
- Positive metacarpophalangeal or metatarsophalangeal "squeeze" test to elicit arthralgia
- Morning stiffness > 30 minutes
- Joint symptoms > 6 weeks (reason enough for referral; RA diagnosis more likely with symptoms > 12 weeks)
- Abnomal ESR, CRP, serum RF, or CCP antibody tests

DOES EARLY INTERVENTION REALLY MATTER?

A metaanalysis by Anderson, *et al* has shown that regardless of DMARD employed, most agents have a greater chance of clinical benefit when they are given earlier in the disease[25]. The concept of an earlier rather than later DMARD intervention has been extensively investigated over the past decade. In a 3 year study, Nell, *et al* have shown that when patients with very early RA (disease duration of 3 months) were treated with DMARD, they demonstrated significantly less disease activity and radiographic destruction when compared with those RA patients treated later (disease duration 12 months)[26]. Many clinical trials, including the COBRA, Fin-RA-Co, and the work of Lard, *et al*[27-32] have clearly documented that even minor delays in initiation of DMARD can have disastrous downstream effects on radiographic outcomes. It should be noted that these results were achieved using conventional DMARD (e.g., sulfasalazine, chloroquine, methotrexate, prednisolone) rather than newer and more aggressive forms of combination DMARD therapy, i.e., higher doses of weekly methotrexate and/or tumor necrosis factor (TNF) inhibitors[11-13]. Recently completed trials of TNF inhibitors in early RA showed not only dramatic clinical benefits (as measured by ACR responder outcomes or disease activity scores), but also a consistent pattern of little or no radiographic progression for up to 2 years for those treated with TNF inhibitors (with or without methotrexate). These studies affirm the importance of prompt treatment, avoidance of DMARD delay, and the need to use the best and most effective agents first[33], so that disease progression can be averted.

FACILITATED ASSESSMENT AND DIAGNOSIS OF EARLY RA

The efforts of many researchers (largely from Europe) have shown that early arthritis clinics can be established with the cooperation of primary care physicians, and timely and accurate diagnosis can be made with the use of a few guidelines (Figure 1[6]). The promise of earlier identification, referral, and accurate diagnosis can now be rewarded with highly effective mono- and combination therapies.

Although most practicing rheumatologists have an interest in early RA, most do not have the time, resources, or inclination to revamp current practices to tackle this unmet need. At issue is whether current data are compelling enough to warrant an overhaul of current consultative practices. The time has come for rheumatologists (solo, group practice, or academic center based) to explore the option of facilitated and focused consultation.

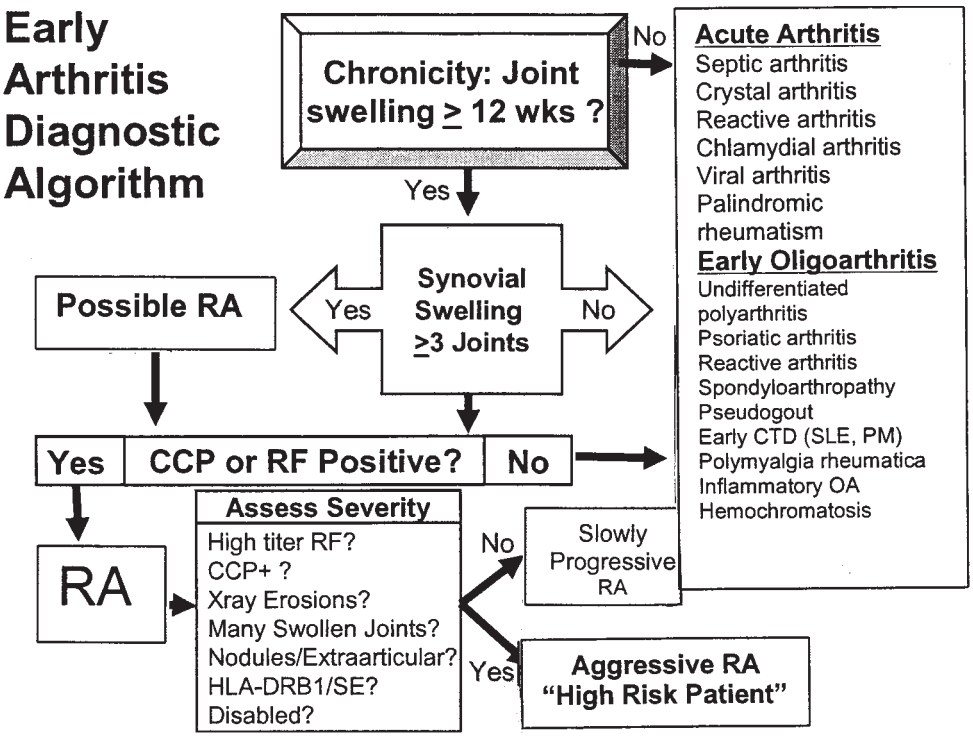

Figure 1. An algorithm for the diagnosis of early arthritis.

While the intent of altering longterm outcomes in RA is hardly novel, the creation of an early RA or early arthritis focused clinic may be daunting for most. Rheumatologists have been frustrated in attempts to change the behaviors of their referring physicians, and some have placed great importance on the need for extensive primary care education in rheumatology. And although primary care physicians may welcome educational efforts in this area, my informal surveys indicate that primary care physicians prefer better access to consultation over better education. The establishment of early arthritis clinics has been enthusiastically received, as the referring physician now has a defined conduit to consultation for patients with new onset symptoms. Interestingly, most rheumatologists feel they already provide such services informally. Yet they fail to recognize that the current shortage of rheumatologists[35] and delays in "routine consultation" are a strong impediment to any consultation, be it early or late. The notion of working smarter and not harder requires that rheumatologists focus time and effort on those who benefit from their expertise.

Facilitated early evaluations will require accurate diagnosis (Figure 1). Also, these new pathways should provide some degree of diagnostic assurance if clinic time and resources are to be restructured. The likelihood of an RA diagnosis appears to be proportional to adherence to referral guidelines (Table 1). Thus, patients with symptom duration of greater than 12 weeks and less than 6 months are more likely to have RA and not nonarticular rheumatic complaints. In addition, the diagnostic algorithm (Figure 1) may be instructive. This algorithm suggests the predictive value of chronicity, polyarthritis, and serologic result in early RA patients. Moreover, subsequent classification of RA patients as having slowly progressive versus aggressive (high risk) disease may prove useful in choosing the most appropriate therapy[36].

Finally, not all clinicians or practice environments can easily absorb the task of early evaluation. Models that have been used to facilitate the initial evaluation of patients with early arthritis are given below. But irrespective of the model, the goal should be easy referral and rapid consultation, i.e., within 2 weeks.

1. Create designated early arthritis time slots that can be filled each week; either with an early arthritis consult — or if unused, such slots can be filled from a pool of patients awaiting future consultation[9].
2. Establish an early arthritis screening clinic to be staffed by physician extenders (nurse practitioners or physician assistants) who can review referral documents and schedule early arthritis patients for assessment, diagnosis, and treatment using defined protocols[37].
3. Ensure appropriateness of consultation. Prescreen early arthritis referrals by asking referring physicians to transmit essential documents, with subsequent review of the record by the rheumatologist to ensure appropriateness of consultation[35].

4. Develop Internet-driven screening measures to capture patient generated symptoms and signs that help to ensure an RA diagnosis, while redirecting those with less qualifying symptoms to usual methods of self-referral.

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