Editorial

Early Arthritis Clinics. Much Early Arthritis Is Unclassified

It has seemed intuitive that evaluating patients during the very earliest phases of arthritis should help us identify factors important for disease initiation and after followup allow identification of prognostic features. The report in this issue by Machold, *et al*[1] is another in a series of potentially useful studies coming from early arthritis clinics that have been functioning mostly in Europe over the last 20 years. Also, in a supplement published in *The Journal* early arthritis clinics are reviewed[2].

Features of early arthritis clinics have varied as to the duration of arthritis that qualifies as "early" and the clinical criteria for entry. The Austrian study by Machold, et al[1] insisted on less than 3 months of symptoms in an attempt to get "very recent onset arthritis." This is to be commended, as other studies have occasionally considered up to 2-3 years as "early." The cut off at 3 months should be able to provide a group in which guidelines for practical management decisions may be useful. Three months is almost certainly not enough to define key initiating steps in pathogenesis, but that was not their intended focus. Some studies have centered only on people felt to have early RA, while this investigation is fortunately more inclusive. Actual entry criteria may however influence findings. For entry in this study, patients had to have either swelling or pain in at least one joint "not related to trauma," plus any laboratory sign of inflammation, which interestingly included elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and peripheral blood leukocytosis or rheumatoid factor (RF). Arthrocenteses were not mentioned, although later diagnoses were to consider exclusions among which crystal diseases might be important.

One of the striking aspects of the study is the apparent effort to classify as many people as possible as "rheumatoid arthritis" (RA) by including individuals with "polyarthritis" without evidence of other inflammatory rheumatic diseases based on laboratory investigation, or people who met American College of Rheumatology (ACR) criteria cumulatively although not all at one time. How useful is this approach? It was striking how well much of this "RA" did. Might it not be more interesting to see if those for whom inclusion criteria were stretched may really have something somewhat different with a better prognosis? Patients with RF who may have more typical RA did have more erosions at one year; this was despite usual treatment by rheumatologists. Maybe early diagnosis did not improve outcomes but included people with "something else" than RA.

I am interested that 16 patients still had undifferentiated arthritis at one year, despite the liberal criteria for RA. Seventeen patients were initially considered undifferentiated but were called RA at one year. It could be important to know what changed the diagnosis and whether these people's course was reflected more by that initial impression or the later diagnosis.

Whatever the answer, I would like to focus discussion on these many unclassified cases. Several series have emphasized the frequency of unclassified arthritis in early arthritis populations, with Hulseman and Zeidler leading thoughts on this[3,4]. Of 217 patients with inflammatory arthritis of less than one year's duration, 117 were considered undifferentiated. These patients in general did well, with 54% of those followed in remission and 7% having evolved into RA. Wolfe, *et al*[5] and Morel, *et al*[6] also noted unclassified cases in their early cohorts. The latter group noted that about 50% later evolved into RA. In the US National Institutes of Health (NIH) early arthritis studies in which I participated, undifferentiated arthritis was a more frequent diagnosis in patients with disease of less than one year's duration than either RA or reactive arthritis[7]. In the study reported here, 219 were entered, but it is noted that at least 59 were lost to followup before one year. What had been their presenting impressions? Maybe this group could be expected to include even more patients who were hard to classify and had better prognoses.

Some have found RF to be an early important predictor of diagnosis and course[8], but Gerber, *et al*[9] studying our NIH early patients (during the first year) found that polyarticular disease was actually a better predictor of poor functional outcome[9]. Antibodies to citrullinated antigens, although not

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widely available, need to be considered for help with diagnosis and prognosis[10]. We and other groups also believe that features of synovial tissue merit consideration as prognostic, but biopsies are usually not available early[11,12]. The role of the shared epitope is still complex[13]. A variety of other studies appropriate to an approach in clinical practice have been reviewed[14].

I like the idea suggested by Machold, *et al* to use the term "early inflammatory arthritis" for some period during early observations of many patients. I do that in our clinics to be sure that we keep thinking about other diagnoses that may have more specific treatments or other systemic implications. Such a term need not delay treatment that can be based more on signs and symptoms than on a name. Perhaps some unclassified cases or others that we believe may have better prognoses still could be treated aggressively with DMARD as these could be the people who will get remissions not "just" 40–50% ACR 50 improvement. This needs to be studied.

As one can probably gather from the preceding comments, I am concerned about the unsatisfactory state of our current classification criteria in general and that of early RA in particular. I have addressed this previously[15-17] and remain concerned that many factors must be considered as influencing the unique course of each person's encounter with an inflammatory process. The factors certainly include a wide variety of genetically determined responses and traits, education, personality, support systems, previous infections and immune responses, how they handle drugs, hormones, etc.[15]. Although many would emphasize that classification criteria should not be used for diagnosis, the concepts in the criteria certainly are used in diagnosis.

The report by Machold, *et al* supports other previous studies that early diagnosis is especially difficult[18], and perhaps we should be looking for different terms for many early patients. In only about 70% of cases in this study were diagnoses "correct" one year later. Earlier work from our group at the University of Pennsylvania with the late John Eisenberg showed that in patients with new knee effusions, diagnoses made by rheumatologists (and even more importantly treatments given) were changed in about 20% by simple synovial fluid analyses[19]. It could be fascinating to see in the study reported here[1] how often arthrocentesis changed impressions. Some early arthritis studies such as our projects at the NIH specifically required exclusion of crystal disease. Our work assessing the ACR criteria in RA[20] would suggest that crystal disease is present in some cases that would meet criteria for RA. Such missed diagnoses certainly might influence outcomes.

Berthelot, *et al*[21] have presented 10 scenarios of early arthritis patients to 25 international experts. Understanding and interpretation of ACR criteria for RA and European Spondylarthropathy Study Group criteria for spondyloarthropathy varied widely. In only one case did all experts agree on classification.

Some points made by Machold, *et al* deserve reemphasis. Patients felt to have RA tended to have more indolent early courses and were referred later than patients with more acute problems. Some patients with RA may not have been referred during the 3 month window even in the well tuned Austrian referral pattern. Referral to specialists may be even slower in North America. These patients did relatively well with standard disease modifying antirheumatic drug approaches, but whether this reflects the treatment or features of patients seen so early is not yet clear. RF, although not unique to RA, did tend to predict more erosions during the first year. Other potential predictors, such as ESR, CRP, and tender and swollen joint counts did not identify those with erosions at one year.

Finally, patients who are difficult to diagnose are often frustrated by the lack of a name to go with their symptoms. Studies to date all suggest that such patients do better. I like to reassure patients that we will keep looking for new clues, but as long as they do not meet criteria for RA or other specific diseases they actually have a better prognosis.

H. RALPH SCHUMACHER, Jr., MD
Professor of Medicine,
University of Pennsylvania,
Chief of Rheumatology,
VA Medical Center, 151 K,
University and Woodland Avenue,
Philadelphia, PA 19104, USA.
E-mail: schumacr@mail.med.upenn.edu

Address reprint requests to Dr. Schumacher.

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