

Editorial

Cases of Early Inflammatory Polyarthritis Should Not Be Classified as Having Rheumatoid Arthritis



The term “rheumatoid arthritis” (RA) is used clinically to describe a destructive symmetrical polyarthritis often associated with the presence of rheumatoid factor (RF) in the serum. Identification of this disorder is important, as it has been shown to have a major impact both on the individual and on society. It is our contention, however, that the label rheumatoid arthritis should be reserved for those with established disease, and that its use in the first few months after the onset of joint swelling and stiffness is inappropriate and should be dropped.

DEVELOPMENT OF CRITERIA

Sir Alfred Garrod coined the term rheumatoid arthritis in 1859. He had discovered the excess of uric acid in the blood of gouty patients, and this enabled gout and RA to be distinguished from one another. Garrod included what we now call osteoarthritis (OA) under his heading of RA. His son, Sir Archibald Garrod, finally made the modern distinction between OA and RA in 1907¹. However, even when the term rheumatoid arthritis had been agreed on, there remained the difficulty of knowing whether everyone was speaking about the same disease.

Like all forms of inflammatory arthritis, RA lacks a pathognomonic sign, symptom, or laboratory feature. Thus the different forms of inflammatory arthritis can only be differentiated from one another by the development of sets of criteria. All existing sets of criteria for RA take the experienced rheumatologist’s opinion as the gold standard with respect to diagnosis. Initial attempts to develop criteria sets in the 1950s and 1960s were based on consensus opinion of a group of experts²⁻⁴. The 1958 American Rheumatism Association (ARA) criteria² identified a hierarchy of certainty of diagnosis ranging from “possible” to “classical”, a distinction that was later thought to be unhelpful. In 1987 a new set of criteria was proposed by the American Rheumatism Association [now the American College of Rheumatology (ACR)]⁵. They were statistically derived using a standardized methodology. The physicians who participated in the development of these

criteria were asked to submit details of patients who, in their opinion, definitely had RA. The participating rheumatologists then recruited for comparison the next patient they saw who had another specific generalized rheumatic disease such as OA, systemic lupus erythematosus, or fibromyalgia. The RA cases had a mean disease duration of 7.7 years and, by definition, were selected as having “typical” disease. Thus the 1987 ACR criteria, by virtue of their derivation, are appropriate to distinguish established RA from other established rheumatic disorders. Their major function over the past 15 years has been to define homogeneous groups of patients for inclusion in clinical trials and longitudinal observational studies. It remains necessary, however, to consider seriously whether criteria developed under these circumstances have any value in classifying patients with recent onset polyarthritis.

PROBLEMS IN DEFINING AND IDENTIFYING EARLY RA

It might be assumed that a patient with the classical hallmarks of RA — symmetrical arthropathy, positive RF, and radiological erosions — has had the same disease since the day of first symptoms; however, this is not necessarily the case. Since 1990 the Norfolk Arthritis Register (NOAR) has attempted to recruit all new cases of inflammatory polyarthritis, arising in an adult population of approximately half a million, based on first attendance at primary care⁶. Patients were seen at registration and annually thereafter. The 1987 ACR criteria were applied after each assessment. Only 38% of such patients could be classified as having RA using the above criteria when first seen⁷. However, 66% of patients satisfied the criteria when applied cumulatively over 5 years from symptom onset⁸. This demonstrates that early inflammatory polyarthritis is indeed frequently “undifferentiated” at onset and may remain so for some time. It is impossible to specify a time by which differentiation will be complete, or before which it cannot have occurred.

Criteria for early RA should be able to distinguish it from other types of inflammatory polyarthritis such as that occur-

ring after infections such as parvovirus, the arthritis seen in association with psoriasis, and other related disorders. Unfortunately, in the few months after onset there are no features that distinguish the various “causes” of inflammatory polyarthritis. In NOAR, for example, we have considered whether subjects presenting with and without psoriasis⁹ following parvovirus infection¹⁰ or following immunization¹¹ can be easily separated by their clinical and laboratory features: They could not. For example, the proportion satisfying the ACR criteria for RA was very similar among patients with psoriasis (49%) and those without psoriasis (47%)⁹. Patients with and without RF were equally likely to have symmetrical disease, at least when judged on the presence of radiographic erosions in hand and foot joints¹². It is thus not possible to distinguish clinically which patients are going to evolve into RA and so it is inappropriate to consider using the physician’s opinion as the gold standard for diagnosing early RA.

It may be hypothesized that certain combinations of genetic and environmental factors may be responsible for triggering inflammatory polyarthritis, but that different combinations of genetic and environmental factors determine whether such polyarthritis differentiates into RA, psoriatic arthritis, a spondyloarthritis, other forms of chronic arthritis, or resolves completely. If this is the case, then it is only appropriate to use the term RA, or indeed any of the other disease labels, when this differentiation process is complete. Too early an assignment will make it difficult to identify these potential genetic and environmental risk factors.

THE DILEMMA POSED BY THE NEED FOR EARLY TREATMENT

The philosophy of treatment of RA has changed considerably since 1987. The treatment used currently is more aggressive and more effective. The aim is to start treatment as early in the disease course as possible, preferably before the hallmarks of established disease such as radiographic erosions have developed. Given that such hallmarks are used as major features on which the classification of RA is made, effective treatment may prevent or at least postpone such a label being applied. There is a need to identify which patients with early inflammatory polyarthritis have the potential to have persistent destructive disease in order to treat them as early as possible, while avoiding inappropriate treatment of those with other forms of arthritis or those destined for spontaneous remission. The use of standard criteria under these circumstances is clearly inappropriate since, by the time the criteria are satisfied, the opportunity for early treatment will have been missed.

USE OF RA CRITERIA TO PREDICT OUTCOME

Thus it may not be appropriate to develop criteria for early RA — first, because probably there is no such condition and, second, even if early RA does exist, the physician cannot recognize it. Nevertheless, there are certain disease features present at baseline that are useful, both univariately and in combina-

tion, in predicting outcome, be it disease persistence, development of disability, or the occurrence and extent of radiographic erosions. In NOAR, for instance, the presence of RF, particularly in high titer, was important in predicting all these outcomes¹³⁻¹⁶.

Inflammatory markers such as C-reactive protein and various clinical features such as the pattern and extent of joint inflammation were also independently predictive¹⁶. Interestingly, the ACR criteria performed much less well in predicting outcome than the multivariate models generated from such observations⁷. The Leeds group have also found that, in the first 3 months of inflammatory arthritis, the ACR criteria have no discriminant value in predicting persistence¹⁷. Similar observations have been reported in a prospective study of an early arthritis cohort from a Dutch population. In that population a model based on combinations of 7 clinical and laboratory variables was significantly better at predicting both persistent disease and erosive disease than the ACR criteria¹⁸. It should be mentioned that no set of predictive criteria has been able to discriminate between individuals destined to develop “ultimate RA” (those with persistent destructive disease) and those not developing RA with the sensitivity and specificity needed to make a confident clinical diagnosis for the purposes of informing treatment decisions.

CONCLUSION

Application of ACR criteria at disease onset is therefore not helpful in separating out a group of individuals with the disease entity RA. More importantly these criteria do not identify patients who are ultimately likely to develop significantly more severe disease than the remainder. Cynically, the only justification for using the ACR criteria, or indeed any criteria to define RA, in patients with early inflammatory polyarthritis is to satisfy the insistence of manuscript reviewers! We believe that, for the majority of patients at the time of presentation, early inflammatory polyarthritis is indeed undifferentiated. Although established RA is one possible outcome, there is no such entity as early RA. Diagnosis is less relevant in this situation than risk prediction. We would argue that it is better to divide patients with early disease into subgroups, categorized by similar risks for specific outcomes. Current attempts at such categorization are based on the presence/absence of factors such as RF either individually or in combination. As science evolves, however, with new antibody tests or better genetic predictors, the categorization rules will vary. The requirement to remain responsive to such changes is important in maximizing the clinical utility of this process.

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