Newly diagnosed rheumatoid arthritis

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We can now affect the natural history of RA

Although the concept would sound heretical in some quarters, rheumatoid arthritis (RA) may now be a treatable disease. The aphorism of 25 years ago that “we don’t treat RA, we manage the patient with the disease” may no longer be operative. Emery and colleagues in this issue of the Annals have made a recommendation (called a “clinical guide”) for how and when primary care physicians can identify patients with suspected RA and refer them to a rheumatologist.1 They state, unequivocally, that the initiation of disease modifying antirheumatic drugs (DMARDs) very early in the course of RA will improve patient outcome and increase long term quality of life. Their paper makes a compelling argument in favour of this recommendation; however, several issues dealt with in the article do raise questions that are in need of additional data and clarification.

THE APPROACH OF EMERY ET AL Evaluation of published reports

The approach of Emery et al was to perform a literature database search and then to use an accepted classification scheme to evaluate published clinical evidence based on the potential for bias to influence the results, giving randomised clinical trials the highest marks and expert opinion the lowest. Well performed observational inception cohort studies appear to have received an intermediate value. The supporting evidence and the proposed clinical recommendation were later circulated among these six wise men for critical evaluation and consensus building. The net result of their efforts is not only a referral recommendation but also a practical clinical tool employed by primary care physicians to identify patients suspected of having RA during the early stages of the disease. The technique for evaluation of early RA, which has recently been validated,2 is based upon a composite compression test of the hand or “squeeze” test, illustrated in the article, for evaluating the tenderness of metacarpophalangeal and metatarsophalangeal joints.

Basis for their recommendations

It is important for the reader to understand the basis for their recommendations. What appears undeniable, after nearly a decade of studies from all over the globe, is that joint damage in RA occurs early3 and at a consistent rate over time.4 However, the rate of development of new erosions in joints not previously eroded appears to be accelerated in the first three years.5 Furthermore, new imaging techniques have the ability to identify damage before it becomes radiographically evident; however, actual validation of this concept (that is, the degree to which the sensitivity and specificity of a magnetic resonance imaging (MRI) erosion can predict a radiographic one) is not yet at hand. The authors point out that studies of synovial tissues from asymptomatic joints contain evidence of cytokine gene expression indicative of active RA inflammation, giving rheumatologists fair warning of things to come later in the disease. Early arthritis clinics (EACs) have now provided us with a consistent clinical story for prognostic features that predict disease persistence as well as risk factors for radiological damage and disability.6 In effect, EACs have shown us that identification of patients with a high probability of receiving value from an early and accurate diagnosis (and hence, treatment) is possible.

DMARD treatment

The major feature of the argument of Emery and colleagues, and one that is perhaps even more compelling, is that prompt institution of conventional DMARD treatment improves outcome and slows radiographic progression of disease in patients with early onset disease, usually defined as ≤2 years of active synovitis. However, this figure, in some studies, is limited to one year.

“Prompt treatment of early onset RA with DMARDs slows radiographic progression”

The evidence is complementary from both randomised clinical trials as well as well performed observational cohort studies from all over the world. A recent delayed DMARD treatment trial (although methodological issues may influence the interpretation of the results) showed that as little as three months’ delay resulted in more radiographic damage for the group receiving delayed treatment than in an earlier treated group, at a two year end point. Ironically, and perhaps quite importantly, most of these data come well before the impact of biological treatments. Nevertheless, there is little question now that biological treatment can not only halt radiographic progression of established disease7 but can also alter the two year trajectory of radiographic damage in patients with early onset disease.8

Does early treatment with DMARDs affect the age of death?

Finally, the authors present what is likely to be the most important argument of all—that is, the impact of aggressive and early treatment with DMARDs on whether patients die earlier if they have RA. Regardless of the fact that North American data continue to show that RA is associated with premature mortality,9 10 European patients identified after 1985 and enrolled in a prospective cohort for 10 years simply do not die any sooner than controls matched for age and sex.11 Although it cannot be proved, it makes good clinical sense to believe that early aggressive management (with conventional DMARDs in almost all cases) is responsible for this effect on RA mortality. In addition to this argument about mortality, the authors gather and present evidence that DMARD toxicity is certainly no worse than that found with long term non-steroidal anti-inflammatory drug use, providing rheumatologists with additional confidence in their approach to patients with early onset disease.

Proposals

Emery and colleagues conclude from the evidence they review that permanent damage occurs early and that early institution of DMARDs slows this damage, improves outcome, and increases quality of life. They propose a reliable and sensitive method for making a rapid diagnosis of RA in the primary care population by defining what they call “clinical suspicion” of RA. This definition includes the “squeeze test” (noted above) as well as morning stiffness >1 hour and more than three swollen joints. Presumably this test will differentiate between RA and other non-inflammatory musculoskeletal conditions. Because raised erythrocyte sedimentation rate, C reactive protein, and rheumatoid factor titres can be negative or normal in this group with early stage disease, their inclusion is not recommended in the definition of clinical suspicion.

WHAT ADDITIONAL EVIDENCE DO WE HAVE FOR THE EFFICACY OF DMARDS?

Is there additional evidence to support the contention of Dr Emery and colleagues, or possibly to urge caution in the
opposite direction? Two recent editorials address the identical subject, one from the USA and the other from the UK. Moreland and Bridges make the assumption that inadequately controlled inflammation will lead to permanent damage, and they consider that diagnosis of RA by referral to a rheumatologist requires “medical urgency”. However, these authors quite appropriately ask which patients should be treated, and with what agent(s)? They state that the evidence does not yet prove that combinations of biological agents with DMARDs are the most appropriate initial treatments. Moreland and Bridges have strong reservations against reliance on primary care for RA management, because waiting for months or years before effective intervention does not provide the best treatment based on what we know today. On the hopeful side they recognise that RA and cardiovascular morbidity/mortality are related, and newer potent treatments might possibly have an impact on cardiovascular morbidity in RA.

Echoing many of the identical thoughts of Moreland and Bridges, and citing the same evidence, Quinn et al make the additional statement that “biological treatments have potential to revolutionise the treatment of early RA.” These authors feel that the benefit received by standard DMARD treatment over placebo or delayed treatment is unquestionable, although they feel, as do Moreland and Bridges, that there is insufficient evidence to recommend combination treatment using both DMARDs and biological agents in all patients at the onset of disease.

LONG TERM OUTCOME OF RA
The 1930s to the 1960s
It is quite remarkable how the long term outcome for patients with RA has changed over the decades. Using standard treatment (bed rest and aspirin) in the 1930s, 1940s, and 1950s, Short and colleagues presided over a relentless progression of disease. In the subsequent decade, modern treatment consisting of gold and corticosteroids from a large metropolitan centre in New York City produced undeniable progression of disease.

“The long term outcome for patients with RA has changed enormously”

An influential study from a tertiary care hospital in London following up a cohort of patients to the mid-1980s almost sounded the death knell for rheumatologists’ efforts; after 20 years of disease, over half of the patients were either dead or severely disabled. However, Scott and associates noted that late presentation to the doctor was a poor prognostic sign, and the time from disease onset to institution of a remittive agent was substantially delayed in this patient group.

The past decade
It is only since we began to follow up truly inception cohorts with recent onset disease in the 1990s that this situation has completely turned around. Numerous publications in the past decade from all around the world (surprisingly, not from the USA) support the concept that early aggressive DMARD intervention (defined, usually, as occurring within the first 12 months of disease) can reduce joint damage, stabilise function, and improve quality of life. The inception cohort study of Kroot et al found statistically significant improvement in the Health Assessment Questionnaire score (a complex variable with different influences over time) over the first six years and no change from baseline at 10 years. It is not possible to demonstrate this effect in usual care situations, where patients enter the cohort at different time points in their disease.

Today
What additional evidence do we have now to support the notion proposed by Emery and colleagues that patients have a better outcome today than 25 years ago? It is difficult to teach our residents today about the extra-articular manifestations of RA when we rarely see them in the clinics or on the hospital wards. Although it is entirely possible that the decline in cigarette smoking may have a long term impact. Boers and colleagues compared a treatment with single dose DMARD treatment. Despite a loss of the incremental clinical effect from the combination group, radiographic superiority remained and persisted. Similarly, Kirwan showed a significant reduction in radiographic progression related to the addition of low dose corticosteroids to standard DMARD management in patients with early active RA. More recently, monotherapy with low dose prednisone was compared with placebo alone for six months in a group with early active disease; after six months, a standard DMARD (sulfasalazine) was added to any patient in either group not achieving a clinically satisfactory response. Although prednisone alone achieved a better clinical response at six months, this was lost at 12 months. In contrast, radiographic scores for joint space narrowing and erosions improved for the prednisone group after six months with a separation between the groups that continued to widen over time. The main message from these clinical studies is not a recommendation that steroids are to be used in early RA but, rather, it is recognition that aggressive control of inflammation early on produces long lasting beneficial effects on joint destruction. The decision to use steroids must be made with more attention paid to the side effects expected and demonstrated in these studies.

LESSONS TO BE LEARNT
What are the special lessons to be learnt from the exercise displayed by Emery and colleagues in this issue of the Annals? At the very least they have exhorted the community of rheumatologists to stand up and be counted. The evidence they cite is convincing, although it might be argued that inception cohort outcome studies carefully carried out do not deserve to be given less value (or be considered more “biased”) than randomised clinical trials of short duration. It appears axiomatic that we now have an opportunity to truly affect the natural history of RA. Whether the surrogate marker of a comparative reduction in a modified Sharp score represents a clinically significant impact on joint destruction, chronic pain, real time functional loss, or the need for joint replacements awaits further evaluation by our colleagues. The new imaging techniques (such as MRI) require validation, and the relative clinical importance of prevention of newly eroded joints versus a change in a modified Sharp score remains to be determined. Furthermore, if early aggressive management should contain combinations of drugs (that is, biological agents and DMARDs), and truly it might, the proper studies are not at hand to make that judgment. Probably in the next two years we will see the results of three-arm controlled trials evaluating the standard of care (either methotrexate or sulfasalazine) compared with the new biological agents, and compared with the biological agents plus the standard of care.

CONCLUSION
If Emery and colleagues are correct about their contention that primary care patients need to be seen sooner rather than later by rheumatology specialists, it
is not sufficient to provide a tool that only specialists know how to use correctly. An expert rheumatologist may be able to squeeze the hand of a patient with synovitis accurately, observe whether or not a joint is swollen, and ask about morning stiffness. However, these authors may underestimate the ability of our primary care colleagues to take the time to perform the task with the same accuracy. If this tool must be administered by a trained metrologist or a rheumatologist, then its primary purpose will be defeated. Finally, and especially if our new treatments are costly for society and have marked side effects, when do we select our patients for this intervention? When does early synovitis (the kind that may and does remit) end and actual early RA (that is, persistent disease) begin? Green and colleagues suggest 12 weeks is the optimal cut off point. Right now, that appears to be the best answer. Lastly, those who control the finances, and thus access to care, need to be convinced that RA treatment has benefit for society. We have more work to do.


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