

Later Comes Earlier, Nowadays

While we deliberate about beginning, it is already too late to begin.

Quintilian, 35-96 BCE

We all agree that early identification and treatment of rheumatoid arthritis (RA) with “tight” control currently provide us our best opportunities to optimize outcomes for patients^{1,2,3,4,5,6,7,8,9,10,11}. At present we seek drug-induced suppression of disease for prevention of inflammatory damage and consequent disability. We expect remissions in half or more patients we are able to treat early. We hope an occasional patient will retain a remission when drugs are tapered and even stopped. We are thrilled to have at least 9 conventional and 9 biological disease-modifying antirheumatic drugs (DMARD) to choose from and combine. However, we are frustrated that we do not have better markers to allow us to select the best therapy for each patient without the trial-and-error process we now utilize. We are disappointed and saddened when treatments fail, and patients suffer rather than benefit from therapy, as still happens. We struggle, too often unsuccessfully, to provide expensive state-of-the-art medications to all we think should receive them.

Early recognition and intervention for RA is one of the triumphs of an age of rheumatology that has truly transformed how we think about caring for patients. There is now urgency in finding RA patients and getting them to rheumatologists or comparable therapeutic programs. We now have new criteria that facilitate early classification of RA¹². The 2010 revised classification criteria provide a framework to identify patients before the progression of disease (by eliminating the requirement of at least 6 weeks of disease or presence of nodules or erosions, and by focusing on the number and site of the involved joints, serologic abnormalities, acute-phase reactants, and symptom duration). Moreover, we have new tools available to quantifiably and reproducibly document the outcomes of our care¹³. These include Disease Activity Score 28 and other composite indices, acute-phase reactants, swollen and tender joint counts, physician and patient global assessments, and the potential use of musculoskeletal magnetic resonance imaging and ultrasound. While each has advantages and disadvantages, their thoughtful use ensures proper monitoring. Indeed, using an objective instrument to assess disease activity is superior to previous conventional and often subjective methods for making clinical decisions. Such tools

are still underutilized in current practice. However, this may change as insurers, including the government, increasingly require them for quality assurance, and as practitioners appreciate their importance. And finally, we have a strict definition of disease remission. This reflects the tender and swollen joint count, C-reactive protein level, patient global assessment score, and the simplified Disease Activity Score¹⁴. Disease control is possible in early RA with the use of conventional DMARD^{3,4,5,6} and with the additional use of biologic anti-tumor necrosis factor agents⁷. Not only has combination therapy been found to be effective, but early, intensive treatment with monthly visits is considered superior to quarterly visits⁶. These changes, slowly percolating into daily practice, are the new paradigm for how we perceive RA and its optimal management.

Why can't we implement this universally now? What must we still know? Or do? The problems are procedural and perhaps also philosophical or even existential. When does disease begin^{15,16}? When exactly is the benefit of early, aggressive treatment lost? What shall we do with individuals without clinical detectable disease who are seropositive for rheumatoid factor or cyclic citrullinated peptides? Is “RA” an oversimplification or a group of heterogeneous syndromes? Are there multiple “RAs”? And, when we decide it's time to intervene, what is best? For how long? What will be the most effective yet safest regimen?

There are potentially rather daunting procedural, logistical, practical, and societal problems too. Some of these are reported by Tavares, *et al* in this issue of *The Journal*; they provide valuable insights¹⁷. For example, the Canadian experience reported that from 2001 to 2003, 91% of patients were started on DMARD therapy within 3 months of the recognition — not onset — of RA. These retrospective data did not mention use of biologic therapies, and infrequently included objective, standardized instruments measuring disease activity. Despite these limitations, these investigators provided a valuable glimpse into the clinical practice of treating early RA in the setting of socialized medicine. Further studies expanding on these preliminary results would certainly be of interest, offering a mirror to others highlighting achievements and failures in practice.

We need to do better. How does a society or community screen a population to find these patients? Absent screening, how is referral information disseminated effectively to primary care providers who would otherwise see these

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patients serendipitously? How do we ensure an adequate number of rheumatologists to promptly accommodate referrals? If we rheumatologists can't do this, are there others who can? Or who can be trained? Unfortunately, we interpret available data as not supporting the notion that non-rheumatologists can do this^{18,19}. And how do we ensure universal access to care? To costly contemporary therapies?

Our own respective experiences illustrate and in part contrast the problems we face and the successes we can achieve. One of us (KDT) with colleagues developed an initiative to provide longterm care for patients with RA in a primarily underserved, immigrant, uninsured, and often transient urban population, at the Rheumatology Clinics of the Los Angeles County (LAC+USC Medical Center) healthcare system, one of the country's largest public systems. This program demonstrates certain challenges in making the benefits of timely, appropriate care available to this patient population (Torralba KD, unpublished observations). In a system where demand for care often exceeds the supply of providers and other resources, patients recognized by their referring physician as having inflammatory arthritis may wait as long as 6 to 12 months before their first general rheumatologic evaluation, usually taking only nonsteroidal antiinflammatory drugs or corticosteroids. Recognition of this problem spurred us to develop an "early RA clinic" in 2008. Once seen by our team, aggressive DMARD therapy is instituted (within budgetary and formulary limits) to control disease as "tightly" as possible by following patients, with appropriate quantifiable metrics, monthly. Although we have not yet calculated health costs to patients and society stemming from their disability and the limitations of our healthcare system to initiate care for them sooner, we believe these to be significant. Patients arguably suffer unnecessary disability, have impaired quality of life, may not be able to work, and they may consume medications and other supportive resources, all subsidized by public funds. Surely this is not tolerated for certain other patients, like those with heart disease or stroke. We must better educate those in leadership: it is cost-effective and socially responsible, if not morally imperative, to do no less for our patients with chronic rheumatic disease.

Another of us (JRO) with colleagues had a different experience, having identified, enrolled in a clinical trial, and begun "disease-modifying" treatment in RA patients (with medications provided by sponsors) within a mean of less than 4 months of onset of symptoms of disease; a consortium of dozens of academic and private practices, the group included at least some indigent patients²⁰. In a recently completed trial, both "triple therapy" (methotrexate, sulfasalazine, and hydroxychloroquine) and methotrexate plus etanercept were equally effective disease suppressants during the first year of therapy. Key to successfully identifying patients and starting them on medication early was the care of committed, available rheumatologists who strongly

believe in early therapy and enrollment requirements of the trial, established collaborative relationships with primary care physicians, and the resources necessary to offer such care to patients.

These preliminary findings, together with the experience of our colleagues in Canada¹⁷, emphasize that prompt, aggressive utilization of conventional, effective, and affordable treatments offers all patients with RA opportunities to achieve full remission early in disease. This is the challenge of clinical practice.

Thus we near a threshold. We are able to control disease activity in the majority of patients with RA and prevent longterm disability if we can find patients with RA at onset of disease, start them on a therapeutic regimen, and reliably measure outcomes. The limitations we face are neither our current art nor science, but rather a lack of communal resources and will. It should be possible; at the very least we can do better. We owe it to our patients.

There are two mistakes one can make along the road to truth... not going all the way and not starting.

Gautama Sikkharta, 563-483 BCE

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