Rheumatoid arthritis (RA) is a common, incurable, and serious disease. The word ‘rheum’ roughly translates from the Greek for ‘flowing,’ and was applied to this condition on the premise that the disease was secondary to the ‘bad humors’ disseminated throughout the body. Although much attention has been devoted to the management of its articular features, it should be appreciated that RA is a systemic disorder with wide-ranging organ manifestations that extend well beyond the joint margins. The study of RA over the past century has taught us that the disease initially presents with joint pain and swelling, but does indeed ‘flow’ throughout the body with subsequent involvement of many organ systems, with wide-ranging clinical effects.

RA is the most common of the inflammatory arthritides, affecting almost 1% of the adult population worldwide. Interestingly, this is a statistic that holds true across many ‘developed’ population groups. The incidence in the US is estimated at 25 per 100,000 population for men and almost double that, 54 per 100,000, for women. It is thought that RA results, directly or indirectly, in 250,000 hospitalizations and up to 9 million physician office visits per year. The disease is seen across all ethnic groups and cultures. A 1998 report noted that, 10 years after the onset of RA, over half of all patients demonstrate significant disability and, as the disease advances to the 15-year mark, only 40% are still working. As recently as 20 years ago, more than half of the 100 RA patients treated in a London referral center were either dead or severely disabled at the 20-year mark, despite receiving the accepted ‘standard of care’ treatment regimen for RA available at that time.

Not only is disability an ever-looming threat, but early mortality is also a real feature. Life expectancy is reduced by an average of three to 18 years with established RA. Surprisingly, the fall in overall mortality rates seen over the past four decades in the general US population has not been similarly seen in those members of the population affected by RA. Recent work has demonstrated that a significant cause of the higher mortality seen in the RA population is due to excess cardiovascular disease. As a group, RA patients suffer more myocardial infarction, cerebrovascular accidents, and even heart failure than those without RA. The direct and indirect costs of this disease, both to the individual patient and to society, are staggering.

The Rationale for Early Therapy
RA, a systemic disease with articular manifestations, causes joint damage and destruction early in its inexorable course. For 20 years we have known that bony erosions, the radiographic demonstration of aggressive disease, occur early in the course of the disease—often within the first one to two years after the onset of joint symptoms. Curiously, these erosions may first occur in the feet, even in the absence of pain or obvious swelling there. Newer imaging modalities, such as magnetic resonance imaging (MRI), have opened our eyes to the fact that joint and bone damage, mediated through synovitis, occurs well before plain films demonstrate the usual erosions so characteristic of RA. MRI can detect bone marrow edema, tendonitis, and synovitis with greater sensitivity than plain films. This MRI damage was seen in a population of patients with early RA (those with symptoms present for less than six months). We now understand that RA damage occurs long before the typical plain-film erosion is identified, demonstrating the importance of intervening earlier in the disease course and, in so doing, affecting the final outcome.

Much of the work expended in studying the various therapies for RA has been performed in populations of RA patients with well-established, long-standing disease. These patients have often had disease for years, with its attendant established damage, bony erosions, and functional compromise (disability). Recent thought about RA management has centered on the concept that ‘early’ intervention—i.e. before erosions
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are seen on plain film or the disease is firmly established—might result in a better outcome in terms of joint damage and consequent disability. The past decade has seen a push toward using remittive therapy earlier and earlier, reversing the older approach of instituting treatment after erosions appeared.16

A prime reason to treat early in RA is that delay in therapy has been shown to adversely affect radiographic outcomes. In the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial, single-agent therapy for RA did not work as well if a delay in institution extended past three to six months from the onset of symptoms.17 An even earlier study, The Combinatietherapie Bij Reumaide Artritis (COBRA) trial, looked at the value of intensive combination therapy in early RA. In this study, the median duration of disease activity was four months. The investigators administered sulfasalazine, methotrexate, and prednisolone (at an initial high dose with a taper to zero at 28 weeks) versus sulfasalazine alone early in the disease course, and showed that combination therapy given early resulted in better clinical and radiographic measures of disease control and suppressed damage progression at 56 weeks.18

More recently, the concept of treating very early RA (VERA—first three months of disease) compared with late early RA (LERA—nine months to 3.5 years of disease) was explored. Twenty VERA patients were matched to 20 LERA patients who waited on average 12 months for disease-modifying antirheumatic drug (DMARD) therapy to be started. At 36 months of treatment, both the disease activity and radiographic damage scores were statistically significantly better in the VERA group.19 Clearly, a delay in treatment has significant later consequences. Nothing is gained by ‘watching and waiting’ when deciding to initiate treatment in a patient with RA. The assumption has to be that early treatment is both important and warranted, and the approach in 2008 should be driven by early treatment. Rheumatologists have now embraced the concept that there is a ‘window of opportunity’ during which aggressive intervention and treatment will likely reap long-term benefits. The hard part has been defining just when that window opens and how soon after opening it begins to close again. For how long after symptoms begin does therapy enhance the preservation of structural integrity and stave off the functional compromise and disability that are the hallmarks of this disease? It is also hoped that early treatment may influence the development of extra-articular features and the increased mortality described in RA.

The concept of a ‘therapeutic window’ opening during the first three months of disease activity is becoming clinically accepted, as is the practice of treating an inflammatory polyarthritis, likely to be RA, early and aggressively in the hope of actually preventing RA, or at least forestalling it. The Probable Rheumatoid Arthritis Methotrexate versus Placebo Therapy (PROMPT) study in The Netherlands randomized 110 patients with undifferentiated arthritis to either methotrexate (MTX) or placebo. Significantly fewer patients given MTX progressed to RA at one year.20 We are seeing, in the clinic, an earlier and earlier start point for the aggressive treatment of RA. One must remember that the trials and studies noted above were performed in the era before biologic therapy (tumor necrosis factor [TNF] inhibitors, rituximab, abatacept, and anakinra) was seeing widespread clinical application. These agents, along with traditional DMARDs, are now being administered earlier and earlier to the RA patient.

The major trials that studied the various TNF inhibitors all demonstrated efficacy when given to patients with early RA. In fact, each of these important studies specifically treated patients whose disease was still in its early stages. The design of each of these pivotal trials incorporated early treatment, recognizing the importance of this approach. The Etanercept in Early Rheumatoid Arthritis (ERA) trial provided strong evidence that early disease suppression—within three years of onset—with a biologic agent resulted in better radiographic outcomes compared with MTX monotherapy.21 The studies of infliximab—the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE)—and adalimumab—A Multicenter, Randomized, Double-Blind Clinical Trial of Combination Therapy With Adalimumab Plus Methotrexate Versus Methotrexate Alone or Adalimumab Alone in Patients With Early, Aggressive Rheumatoid Arthritis Who Had Not Had Previous Methotrexate Treatment (PREMIER)—were both characterized by administration of a TNF agent to patients with RA of less than three years’ duration.22,23

Early Diagnosis

If we accept that early therapy is important, and a worthy goal, we must be sensitive to its early diagnosis. An increased sensitivity to the presence of this disease is offered by utilizing a newer assay—the development of antibodies against cyclic citrullinated peptide (anti-CCP). These antibodies are now recognized as offering increased specificity for RA with similar sensitivity to the presence of rheumatoid factor (RF).24 Anti-CCP antibodies form against modified proteins containing citrulline, a post-translational modified arginine residue, and are detected via a standardized enzyme-linked immunosorbent assay (ELISA). A significant number of patients who do not fulfill strict American College of Rheumatology Classification Criteria for RA but who are seropositive for anti-CCP will go on to develop RA.25 Clearly, anti-CCP positivity is a strong predictor for the development of RA.

A New Paradigm of Management

Although it is increasingly accepted that aggressive treatment of RA should commence early, the question to be answered is how that therapy should be constituted. What drug or combination of drugs works best? The BeSt trial (Behandel Strategieen, Dutch acronym for ‘treatment strategies’) attempted to find the optimal drug or combination of drugs, including biologic therapy in the form of infliximab, to answer that very question. This study randomly assigned 508 Dutch patients with RA of less than two years’ duration to one of four treatment strategies often
used by rheumatologists in the real-world clinical setting. Treatment changes were decided upon in advance and were predicated on whether patients achieved a standardized disease activity score (DAS) that reflected minimal disease activity.

The four treatment strategies consisted of:

- **group 1** (sequential monotherapy)—this group began with MTX, which was then supplanted by sulfasalazine, then leflunomide, and then MTX plus a TNF inhibitor if disease control was not achieved;
- **group 2** (step-up therapy)—this group began with MTX and then added on combination therapy singularly beginning with sulfasalazine, then hydroxychloroquine, then prednisolone, and finally a TNF inhibitor with discontinuation of sulfasalazine and hydroxychloroquine;
- **group 3** (initial combination DMARD plus prednisolone)—this group received an initial high-dose course of a corticosteroid along with MTX and sulfasalazine; in this group, persistent disease activity warranted the addition of cyclosporine (with the sulfasalazine discontinued) followed by methotrexate (with the prednisolone discontinued); and
- **group 4** (combination MTX and a TNF inhibitor [infliximab])—this group began treatment with combined MTX and infliximab, but persisting disease activity resulted in the addition singularly of sulfasalazine, leflunomide, and, lastly, a combination regimen of MTX with cyclosporine and prednisolone.

This study was a major contributor to our understanding of how ‘best’ to treat patients with RA. At one year of treatment, a significantly greater proportion of patients in groups 3 and 4 were still on their initial treatment regimen and had earlier clinical improvement and less radiographic progression. When the study was carried out to a second year, there was definitely less radiological progression in groups 3 and 4. Our ‘take-home’ messages from the BeSt Study thus include the need to treat RA early—certainly within two years of symptom onset—almost always with MTX, that excellent disease control can be achieved with frequent and necessary medication adjustment(s), and that the combination of MTX and a biologic agent is very efficacious.

Although the BeSt investigators defined early RA as within two years of disease onset, we know that it makes sense to treat RA early—probably within three months of symptom onset. The practicality of diagnosing RA early and having these patients seen expeditiously by a rheumatologist is difficult to say the least, but it is a worthy goal. Rheumatologists have become more aggressive in diagnosing and treating RA early, so a critical step is having the patient seen by a rheumatologist early in the disease course and not waiting months for a routine ‘new patient’ appointment. Developing ‘early arthritis clinics’ may be an answer to this dilemma. Such centers are evolving in various forms: some use physician extenders to screen new referrals for likely RA patients, while some rheumatology clinics set aside a certain number of new patient appointments each week to accommodate the early polyarthritis patients who will most likely have RA and warrant immediate treatment.

Conclusions

RA is a serious disease that should be identified and treated early in its course, otherwise disability and increased mortality ensue. Rheumatologists are now using terms such as VERA or simply ERA when symptoms have been present for less than 12 weeks. Ideally, early treatment should commence within three months of disease onset. Testing for anti-CCP antibodies in patients with polyarthritis allows early identification of probable RA and argues for the initiation of treatment. Constant adjustment of medications following diagnosis to best effect disease control is paramount.