Rheumatoid Arthritis: A Whole New Ball Game

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Rheumatoid arthritis (RA), traditionally, has been a difficult and discouraging condition for medical practitioners to treat. In general, physicians have been taxed to contend with the overwhelming physical destruction, as well as the sometimes devastating medical complications, seen in the disease. Our medical schools do not provide sufficient preparation, giving us inadequate tools for recognition of joint disease in general and few tools for following and monitoring disease progression.

Only 10 years ago, the treatment plan for RA was a leisurely-paced pyramid of medications. It began with nonsteroidal anti-inflammatory agents (NSAIDs), and flowed through empirical remedies such as gold salts and chloroquine, into newer empirical remedies co-opted from cancer treatment or transplantation, such as methotrexate or imuran in recent years.

Over the last five to 10 years, modern studies have contributed to an evolving understanding of the disease. It is now evident that the diagnosis of RA amounts to a prediction of joint inflammation that will inevitably evolve to joint damage, leading to X-ray evidence of erosion and joint space narrowing. Furthermore, these X-ray changes are markers for loss of function and disability. The evolution of X-ray change over time is constant (Figure 1). It does not wane in later years, nor is it accelerated or delayed at the beginning of the disease.[1] After five years of disease, only 25% of patients still retain normal functional status. Forty percent are functional class two, meaning that they no longer work, and the remainder is more severely impaired.[2] Furthermore, RA has been shown to shorten life. Wolfe *et al.*, using ARAMIS data in a prospectively followed cohort, demonstrated that the standardized mortality ratio for RA patients in Saskatoon was 2.24 times that of the general population[3] (Figure 2).

This new understanding of the relentless progression of RA was accompanied by recognition of a possible "disconnect" between the process of inflammation and the process of erosion and destruction. Control of inflammation does not necessarily guarantee that joint damage will not progress. Furthermore, Conaghan *et al.*, with MRI and ultrasound visualization of joints, have demonstrated that the physical examination often underestimates the degree of inflammation that remains in patients we believe to be under control.[4,5]

Taken together, this suggests that RA must not be treated as a disease with leisurely progression. Tsakonis *et al.* demonstrated that a delay of even six months between the time of diagnosis and the initiation of Plaquenil (hydrochloroquine) leads to joint damage that is never regained.[6] Even two years later, patients subjected to a six-month delay show a greater level of damage relative to patients who received immediate treatment. Other studies have demonstrated the same fact: that a diagnosis of rheumatoid arthritis is a semi-emergency. Patients must be treated immediately and effectively from the moment of diagnosis, and diagnosis-delayed damage is never retrieved.

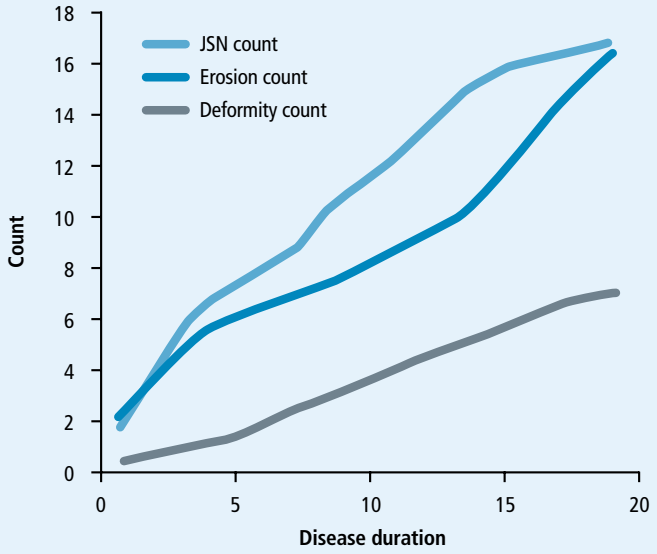
Consequently, it has been proposed that the pyramid should be inverted. Multiple disease-modifying antirheumatic drugs (DMARDs) could be instituted for immediate disease suppression in the early stages, and then gradually removed. At the very least, trials have shown added benefit to combinations, such as methotrexate with cyclosporin, or methotrexate with plaquenil and sulfsalazine.

Treatment Options for Rheumatoid Arthritis

Only four years ago, the pharmaceutical industry focused on RA for the first time. Leflunomide (Arava), a pyrimidine inhibitor, was shown in clinical trials to retard erosions and induce remissions with equal efficiency to methotrexate. The

Figure 1

Radiographic Progression of Joint Erosion and Deformity in Rheumatoid Arthritis Patients



JSN = Joint Space Narrowing

Source: Wolfe, Sharp. Arthritis Rheum 1998;41:1571.

drug causes diarrhea in some patients, and can cause significant hepatotoxicity if not monitored carefully. It was the second drug in history that was invented, marketed and found effective for RA. The first was sulfsalazine, a medication initially marketed for inflammatory bowel disease until it was rediscovered for its original intention years later.

Two years ago, the first tumour necrosis factor (TNF) antagonist, etanercept (Enbrel), was introduced to the market. TNF is a single chain peptide, produced by marcrophages upon phagocytosis of an antigen. It upregulates CD4 (T-helper) cells, B cells and fibroblasts. It activates IL-1, another lymphokine, leading to pannus formation and erosion. Levels of TNF are very high in synovial fluid of patients with RA, and for the first time we have a specific intervention. Etanercept is a TNF receptor fusion protein, linked to an IgG Fc fragment. The agent inactivates TNF before it can reach its cell surface target receptor. It surpassed the effectiveness of all other DMARDs to date, giving an ACR20 response score of 60–70%. The cost: about $15,000 per annum!

Meanwhile, two other agents have come to market. Infliximab (Remicade)—a chimeric (part mouse, part human) antibody to TNF—is quite effective and potent. Given intravenously every six to eight weeks, it has been shown to dramatically retard development of erosions. The main concern with this medication is an increased reactivation of tuberculosis. Health Canada has just issued a notice of compliance for an anti-Il-1, Kineret. Kineret is given daily by subcutaneous injection, and has been shown to dramatically retard the evolution of erosions, an effect that accelerates with increasing use. Kineret seems to be associated with few infections or adverse events, although injection site reactions occur frequently, at least at the beginning of use.

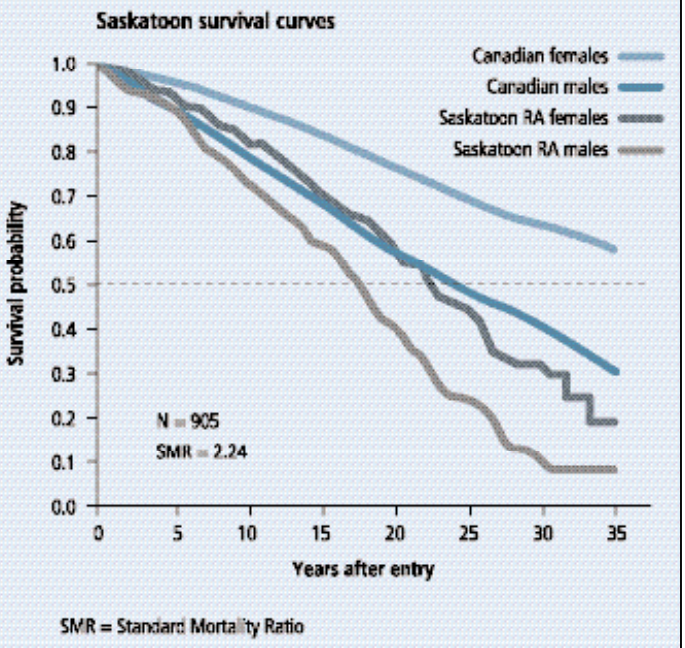
All of these agents are similarly priced to etanercept. New products include D2E7, a human anti-TNF antibody given once every two weeks that looks very promising, and trials are just beginning of oral agents called Map-kinase inhibitors. These monoclonal antibodies and receptor antagonists all arise from a growing understanding of the pathogenesis of RA. Certainly, they all retard inflammation. What is more dramatic is the novel degree of retardation of erosions.

Patients with RA must be recognized and treated early to gain maximum benefit from this new era in therapeutic strategy. There are currently only 270 rheumatologists in Canada, and at least 300,000 diseased patients. Family doctors are at the frontier of early disease recognition. Do they have the tools? Studies suggest that there is a real discomfort among family practitioners with regards to treating arthritis.[7] This is not surprising. Undergraduates in medical school receive only eight to 12 hours of clinic time in the recognition of arthritis! We need to do better.

We are now turning a corner. RA is still a devastating disease, but earlier and more effective treatment is changing the landscape. The wind-swept, bed-confined, systemically ill RA patient is becoming an image of the past. Access to RA medications is the new major issue of contention. Who pays for these expensive new agents? How do we recognize these patients and get them treated in a timely manner? Careful planning and strong leadership will be required in order to address these important issues. ◆

Figure 2

Mortality in Patients with Rheumatoid Arthritis



Source: Wolfe et al., Arthritis Rheum 1994;37:481.

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