

Recent Therapeutic Advances in the Treatment of Rheumatoid Arthritis

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Rheumatoid arthritis is a systemic disease which targets the joints as well as other organ systems. It is the most prevalent of the inflammatory arthropathies and is estimated to affect about 1% of the world's population. The clinical presentation is varied, but most patients have a progressive disease that leads to joint destruction and the associated disability if left untreated. There is significant morbidity associated with some of the extra-articular manifestations of the disease including pulmonary disease, osteoporosis, inflammatory eye disease, and in rare cases a systemic vasculitis. Recent studies have highlighted the role of chronic inflammation in the development of cardiovascular disease which leads to excess mortality in patients with rheumatoid arthritis.

Rheumatoid arthritis is thought to occur in a genetically susceptible host in response to some antigenic trigger. While the factors that initiate this process are poorly understood, the pathogenesis of the disease is beginning to be understood. Pathologic changes in the joint begin in the synovial lining of the diarthroidal joints. Early pathologic changes include neovascularization and thickening of the normally thin and delicate synovial membrane. There is infiltration of the tissues with leukocytes, increased expression of adhesion molecules, proteolytic enzymes, and cytokines and other inflammatory mediators. Together, these factors lead to the development of a pannus, a localized tissue that invades articular cartilage, bone, and the supporting structures of the joint.

It has been known for some time that joint damage can occur early in the course of the disease, and a majority of rheumatoid arthritis patients have erosion of bone within the first 2 years of disease onset.¹ It has also been established that treatment with disease modifying antirheumatic drugs during this early phase of rheumatoid arthritis can result in improved outcomes.² An appreciation of the importance of early intervention prior to the development of erosive disease has led to an algorithm of early detection and aggressive intervention. However, until recently

the therapeutic options were limited to single or combination therapies with only modest benefits in most patients. Medications such as intramuscular gold, cyclosporine, azathioprine, sulfasalazine, hydroxychloroquine, and methotrexate

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comprise the majority of oral agents used to treat rheumatoid arthritis, yet only hydroxychloroquine, sulfasalazine, and methotrexate are currently in wide use. Combinations of oral therapies may be beneficial in some patients, and the addition of a newer oral agent, leflunomide, has added to the armamentarium of therapeutic options. Despite this, oral therapies are clearly inadequate for the majority of patients with rheumatoid arthritis.

Although the precise etiology of rheumatoid arthritis is not known for certain, significant advances in understanding the pathogenesis of the disease have led to new and more effective therapies. The most significant breakthrough over the last 10 to 15 years has been the development of the tumor necrosis factors (TNF) - inhibitors Etanercept, Infliximab, and Adalimumab. Each drug has a unique mechanism of action, but they all inhibit the biologic action of TNF, a cytokine known to play a role in the pathogenesis of joint inflammation in rheumatoid arthritis. Tumor necrosis factors has myriad effects that may

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initiate or perpetuate inflammation in rheumatoid arthritis including regulation of other proinflammatory cytokines, growth of new blood vessels, activation of endothelial cells and osteoclasts, and induction of metalloproteinases. Etanercept is a fusion protein of a TNF receptor linked to the Fc portion of IgG1. Its action prevents TNF from interacting with cell surface receptors. Infliximab is a chimeric mouse/human monoclonal antibody which binds TNF, thus inhibiting its biologic activity. Adalimumab is a fully humanized monoclonal antibody which has a similar mechanism of action to Infliximab. These drugs have had a profound impact on the ability to treat patients who had previously shown little or no response to traditional disease modifying antirheumatic drugs. Numerous studies of these agents have confirmed their ability to control signs and symptoms of disease, improve quality of life, and retard, or in some cases halt, the progression of erosive disease. Clinical studies also indicate that the combination of TNF inhibitors with Methotrexate yields better outcomes than either drug alone.³

Despite the therapeutic advances demonstrated by the TNF inhibitors, there remains a subset of patients who have an inadequate response to available therapies. These patients may continue to have evidence of disease activity with tender and swollen joints or may have progressive radiographic changes despite a good clinical response. Two newer agents approved by the FDA, Abatacept and Rituximab, may be effective with these patients. Abatacept is a T cell inhibitor which acts by blocking the second signal necessary for effective T cell stimulation. Rituximab is an anti-CD20 chimeric monoclonal antibody

which selectively depletes pre-B, naïve, mature, and memory B cells, leaving stem cells and mature plasma cells unaffected. Both drugs, given by intravenous infusion, have been shown in well-controlled clinical trials to decrease signs and symptoms of rheumatoid arthritis as well as retard the structural progression of the disease.⁴

Research and investigation of the next generation of biologic therapy continues with agents aimed at new targets. Anticytokine therapies targeting IL-1, IL-6, IL-15, and IL-17 are currently under development. Tocilizumab, an anti-IL-6 monoclonal antibody, is currently in phase III clinical trials for rheumatoid arthritis, and preliminary results suggest that it has good efficacy. In addition, second generation drugs targeting TNF and B cells are also in clinical trials. Some investigators believe that gene therapy may someday play a role in the treatment of the most aggressive disease, but there are many hurdles to overcome.

Primary care physicians are often the first point of care for patients with early rheumatoid arthritis. With the recent advances in understanding the importance of early diagnosis and aggressive management of the disease, primary care physicians are in a position to take that knowledge and apply it to clinical practice. It is critical to consider the diagnosis and pursue the workup since intervening early can make a significant impact on the long-term outcome. Working closely with their rheumatology colleagues and remaining vigilant for signs of early inflammatory joint disease, the primary care provider plays a most important role for patients with rheumatoid arthritis. **NCMJ**

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