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The role of biologicals in early rheumatoid arthritis

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Recent emphasis on early diagnosis and treatment of rheumatoid arthritis (RA) to improve long-term disease outcome has raised important questions about optimal therapy for early RA. With an expanding armamentarium of disease-modifying antirheumatic drugs including biological agents, there are now several therapeutic choices available to clinicians. However, at early stages of arthritis, difficulty in accurately predicting individual prognosis and response to therapy continues to pose a significant challenge. Future research in biomarkers of progressive, erosive disease and controlled trials to establish the most effective therapies in early RA will greatly enhance our ability to minimize the impact of this potentially disabling disease.

Key words: early rheumatoid arthritis; disease-modifying antirheumatic drugs; biological agents; erosive disease.

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder with the potential to cause destructive joint disease, significant disability and increased mortality.[1] The onset of articular damage can begin early and progress rapidly. Radiological evidence of bone erosions and cartilage damage can be apparent within the first few years of disease by radiograph[2,3], and within months if sensitive magnetic resonance imaging (MRI) techniques are applied.[4] Functional disability may also develop early in RA[5], further underscoring the importance of early therapeutic intervention to prevent poor disease outcome. Hence, in the last two decades, there has been a major shift from the 'wait-and-see' paradigm of treatment towards consensus for early aggressive intervention to control inflammation and preserve function and quality of life. The recognition in

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the mid to late 1980s of the relative safety and efficacy of methotrexate (MTX) facilitated this transition. In fact, MTX has emerged as the first-line treatment for RA and the 'gold standard' against which new drugs for RA can be evaluated and compared. Furthermore, the combination of MTX with one or two additional disease-modifying antirheumatic drugs (DMARDs) conveys a cumulative benefit above and beyond MTX alone.[6–8] These agents can be added in sequence (a 'step-up' approach). Alternatively, a 'step-down' approach can be utilized in which 'induction' therapy with multiple agents is followed by withdrawal of individual drugs as in the Combinatiettherapie Bij Reumatoide Artritis (COBRA) trial.[8]

In recent years, advances in biomedical science have been successful in bringing our understanding of inflammation at a molecular basis into the arena of therapeutic intervention. In-vitro studies have confirmed the critical and potent role of several inflammatory cytokines in the rheumatoid synovium.[9] These inflammatory mediators act in concert to promote bone and cartilage destruction and induce systemic cachexia. Hence, they provide important therapeutic targets for intervention in RA. Indeed, the development of biological agents to counteract the effects of tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) has been heralded as a major breakthrough in the treatment of RA and other selected inflammatory disorders. They represent the first therapies for RA that have a well-defined mechanism of action, each inhibiting a single cytokine relatively proximal in the inflammatory pathway. These biological agents have been shown to rapidly reduce disease activity and improve radiological outcomes in patients with established, active RA when used alone or in combination with MTX.[10–12] In general, the effect of each of the three TNF inhibitors approved by the Food and Drug Administration (FDA) has proven to be more potent than the only available IL-1 inhibitor.

With this growing armamentarium of DMARDs, including both traditional and biological therapies, there are exciting opportunities for devising new treatment strategies for better control of inflammatory arthritis.

With the recognition that irreversible joint damage begins early in disease, attention is now focused on therapeutic intervention very early, perhaps even before the diagnosis of RA can be established definitively, with the goals of achieving long-term control of synovitis and possibly even complete remission. However, a myriad of complicating issues makes this a challenging task. First, in patients with very early arthritis, diagnostic and prognostic markers that will distinguish those destined to develop persistent erosive disease (i.e. RA) from those with a self-limited process have not been fully established. Given our current tools, months may elapse before there is certainty of the diagnosis of RA. Secondly, because of the variability among patients in the length of time from onset of symptoms to diagnosis of definite RA, the definition of 'early' RA has not been agreed upon. For the purposes of this chapter on biological agents, we will define 'early RA' as disease duration of less than 3 years since this definition was utilized in early RA clinical trials with biologicals, but it is likely that the optimal time of intervention is within weeks to months of the onset of symptoms. Finally, if early RA is to be managed appropriately, timely access to specialist care is crucial. However, the current climate of inadequate numbers of rheumatologists makes this approach challenging.[13]

These dilemmas have been discussed in detail in earlier chapters and underscore the difficulty that clinicians face in deciding whether to use potentially toxic medications at very early stages of inflammatory arthritis or to wait until the diagnosis of RA is secure. In this chapter, we will discuss the available evidence for the role of biological agents in