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This issue of *Therapeutics and Clinical Risk Management* contains two interesting and thorough review articles on the use of anti-tumor necrosis factor (TNF) monoclonal antibodies (mAb) in the treatment of rheumatoid arthritis and related disorders. The arthritic diseases and distressing conditions associated with significant morbidity are typified by reductions in functional capacity and quality of life with attendant substantial healthcare expenditure. Development of specifically targeted biological agents in recent years has greatly enhanced the therapeutic options for the treatment of the arthritic diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF is an attractive biological target as it has been implicated as a major pro-inflammatory player in a wide range of other conditions, in addition to the arthritic diseases, including inflammatory bowel disease (D'Haens and Daperno 2006), asthma (Cazzola and Polosa 2006), and other autoimmune diseases (Chatzantoni and Mozaki 2006). Levels of TNF are elevated in the relevant sites of inflammation in these conditions; eg, in the synovial fluid and sera of patients with active rheumatoid arthritis. TNF is a potent osteogenic cytokine and is the central mediator of inflammation and joint destruction in rheumatoid arthritis. Three TNF antagonists are currently available: infliximab, a chimeric anti-TNF mAb; adalimumab, a fully human anti-TNF mAb; and etanercept, a recombinant soluble p75 TNF-receptor-Fc fusion protein. Although there are no clinical studies that directly compare etanercept, infliximab, or adalimumab in the treatment of rheumatoid arthritis, data from noncomparative trials suggest that all have similar therapeutic efficacy.

Etanercept was the first biologic response modifier to be approved by the US Food and Drug Administration for use in rheumatoid arthritis. It acts by rendering TNF biologically inactive through competitive binding thereby preventing the binding of TNF-α and TNF-β to their specific cell surface receptors. Boulos Haraoui and Vivian Bykerk provide a comprehensive review of five major rheumatoid arthritis clinical trials that examined the efficacy and safety of etanercept given either as a monotherapy or in combination with methotrexate. The authors conclude that etanercept is a safe and effective therapy for rheumatoid arthritis. Etanercept reduces not only disease activity, but also limits progression of joint damage in early and late disease. Although etanercept was effective as monotherapy, combination with methotrexate appeared most effective in terms of reducing joint damage. Safety data from the clinical trials detailed in the review have shown etanercept to be well tolerated by the majority of patients.

Adalimumab is a fully human, high-affinity, recombinant immunoglobulin G1 (IgG1) anti-TNF mAb. Engineered using phage display technology, adalimumab is composed of human-derived heavy- and light-chain variable regions and human IgG1 constant regions. Adalimumab is identical in structure and function to human IgG1; it therefore has a low potential to cause adverse immune-based reactions and has a longer half-life than etanercept. In his article, Philip Mease discusses adalimumab in considerable detail. He provides insight into its usefulness; mainly in clinical trials in patients with rheumatoid arthritis, but also in psoriatic arthritis and ankylosing spondylitis. Adalimumab has wide-ranging antiinflammatory effects in these conditions, down-regulating levels of pro-inflammatory cytokines, matrix metalloproteinases (MMP)-1 and MMP-3, and expression of the endothelial adhesion

molecules responsible for pro-inflammatory leukocyte migration together with the modulation of TNF's effects on osteoclast maturation and activation. The author concludes that adalimumab has a rapid onset of action, sustained efficacy with long-term treatment, and shows significant improvements in patient physical functioning and quality of life measures. Overall adverse events were low with few patients discontinuing treatment.

One important issue concerning the use of anti-TNF biologics is that the pro-inflammatory mechanisms that they inhibit are important in maintaining tuberculosis in the latent phase (latent tuberculosis infection [LTBI]). LTBI is associated with the granuloma formation that normally compartmentalizes but does not kill *Mycobacterium tuberculosis*. There is considerable evidence that links reactivation of LTBI to the use of anti-TNF monoclonal antibody treatments; an effect that can be explained, in part, by directly neutralizing TNF, which plays a key role in tuberculosis immunity. It is now widely accepted that patients considered for anti-TNF biologic therapy need to be comprehensively screened and treated for LTBI by clinical specialists in TB before commencing anti-TNF treatment, thereby preventing reactivation in the majority of patients (Keane 2005). Most instances of *Mycobacterium tuberculosis* re-activation were associated with infliximab, but etanercept and adalimumab may also be associated with an increased risk of tuberculosis. Furthermore, histoplasmosis, listeriosis, aspergillosis, coccidioidomycosis, and candidiasis have been associated with anti-TNF usage, but the causative relationship is not clear. As with other immunosuppressant drugs, anti-TNF biologics are contraindicated in patients with active infection (Rychly and DiPiro 2005).

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