BIOLOGIC THERAPY OF PSORIATIC ARTHRITIS

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SUMMARY

Psoriatic arthritis is now recognized as a potentially serious and disabling disease. Traditional therapies have not been very effective in controlling signs and symptoms or preventing progression of damage. Based on the pathogenesis of the disease new therapies have been introduced, particularly anti-TNF agents and anti-T cell agents. Several of those have shown excellent responses in clinical variables, health related quality of life and function, and in preventing radiological progression. However, not all patients have responded, and the long-term safety of these drugs remains unknown.

Key words: Psoriatic arthritis, treatment, biologic agents

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor (1). Some 50% of patients with PsA have spinal involvement including sacroiliitis with or without syndesmophytes. Other features of the disease include dactylitis, enthesitis, as well as other extra-articular features of the seronegative spondyloarthridites. The disease affects men and women equally, usually in the 4th decade. It affects peripheral joints, with a predilection for distal interphalangeal joints. PsA often presents with oligoarthritis in an asymmetric distribution but commonly evolves into polyarticular disease (2). It has been noted that the symmetry is a function of the number of joints involved (3). PsA is now recognized as a potentially severe form of arthritis leading to joint destruction and disability, as well as increased mortality risk (4). Several investigators have demonstrated that polyarticular disease at presentation is a predictor for progression of clinical and radiological damage (5). Thus, it is clear that patients with PsA should be treated aggressively. The question arises: what should patients with PsA be treated with?

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The pathogenesis of PsA is not fully elucidated. However, it is recognized that genetic, environmental and immunologic factors play a role. Whereas genetic and environmental factors are not readily amendable to modification, immunological factors may be. T lymphocytes, particularly CD8+ cells, are thought to play an important role in the pathogenesis of both the skin and joint manifestations of PsA. These activated T cells likely contribute to the enhanced production of cytokines noted both in the synovial fluid and synovial cultures from patients with PsA (6). These cytokines, including IL-1β, IL-2, IL-10, IFN-γ and TNF-α, induce proliferation and activation of synovial and epidermal fibroblasts, leading to the fibrosis reported in patients with longstanding psoriatic arthritis (7, 8). Ritchlin et al. (9) demonstrated that PsA patients with erosions produced more osteoclast precursors (OCPs) compared to healthy controls, and their cells produced OCPs without exogenous RANKL. PsA cells also excreted more anti TNF-α than healthy control cells. Immunohistochemistry studies of subchondral bone and synovium revealed RANK positive perivascular mononuclear cells and osteoclasts in the PsA specimens. RANKL expression was increased in the synovium whereas OPG was restricted to the endothelium. Treatment with anti-TNF agents lead to reduction in osteoclast precursors and lower RANKL production (9). Thus inhibitors of TNF would be appropriate agents to be used in PsA. In addition, agents which interfere with T cells may be ef-

fective in controlling skin and joint manifestations of PsA (10).

In order to evaluate therapies in PsA appropriate assessment tools must be used. Assessment tools used in PsA include the Psoriatic arthritis Response criteria (PsARC), the American College of Rheumatology (ACR) response criteria 20, 50 and 70, and the European response criteria [reviewed in (11, 12)]. Several studies used the assessment of dactylitis and enthesitis using instruments which had not been validated. The assessment of skin disease has generally been based on the Psoriasis Area Severity Index (PASI) or an assessment of a target lesion.

Traditional disease modifying anti-rheumatic drugs have not worked well in PsA (13). The effect sizes for most of these drugs have been low (14). In contrast, effect sizes for anti-TNF agents have been very high, suggesting that these drugs are quite effective for PsA. There are now several anti-TNF agents available for the treatment of PsA. These have been approved in a number of countries for this indication. The soluble receptor for TNF p75, etanercept was the first to be studied in PsA. Both phase 2 and phase 3 trials have shown a remarkable improvement in both the PsARC and the ACR20 response (15, 16). Etanercept was also shown to significantly improve health related quality of life and function using the SF-36 and the HAQ questionnaires. Moreover, the drug was shown to retard progression of radiological damage measured by a modification of the Sharp method. Phase 2 and phase 3 trials of the anti-TNF chimeric antibody infliximab in PsA have also demonstrated remarkable improvement in both skin and joint manifestations, including dactylitis and enthesitis (17, 18). Infliximab therapy was also associated with reduction of progression of radiological damage, measured by the van der Heijde modification of the Sharp method, and was also effective in improving health related quality of life and function (19). The humanized anti-TNF antibody, adalimumab, was also effective in controlling signs and symptoms of PsA, and also prevented progression of radiological damage (20). It also improved health related quality of life and function.

Two anti-T cell agents have been studied in PsA. Efalizumab, the anti CD11a antibody which has been proven effective for skin psoriasis, was totally ineffective in PsA with 28% of the drug treated patients demonstrating an ACR20 response as compared with 19% of the placebo treated patients. On the other hand, another T cell agent, the LFA3 soluble receptor alefacept has demonstrated the same magnitude of ACR20 response in patients with PsA as the anti-TNF agents (21). Unfortunately radiographs were not included in the trial and thus the effect of this agent on radiological progression cannot be determined.

Several other biologic agents are currently under investigation for PsA (10). Although the biologic agents have shown efficacy in PsA, not all patients have improved. Using the ACR20 there are still some 40% of the patients who do not respond. Moreover, the number of patients who demonstrate clinically important improvement of ACR50 or ACR70 is not large. Thus, while the biologic agents have certainly improved the lives of many patients with PsA, there is still a need for new therapies. While these medications appear to be relatively safe in the short-term, it remains to be determined how safe these drugs will be with continued use. Recent studies in rheumatoid arthritis suggest that there is an increased risk of malignancy. However, there is a background increase malignancy risk in rheumatoid arthritis, which is not the case in PsA. Careful follow-up of patients with PsA receiving biologic therapy is therefore required to address these issues. It is recommended that patients be followed in registries so that any signal for toxicity is picked up early.

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