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Tacrolimus in Patients with Rheumatoid Arthritis

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Developing new therapeutic strategies that target the range of cells involved in the pathogenesis of rheumatoid arthritis (RA) is of critical importance. Tacrolimus inhibits T-cell activation and subsequent production of inflammatory cytokines, leading to suppression of bone/cartilage destruction and joint pain in patients with RA. Moreover, it appears to induce osteogenic and chondrogenic differentiation, which may promote repair of destroyed bone and cartilage. T cells are believed crucial in the early and later stages of synovitis. The primary benefit of tacrolimus in patients with RA is likely to be its positive effect on the control of joint-bone erosion.

On the basis of clinical trials to date, tacrolimus monotherapy appears to have some usefulness in active disease resistant to, or intolerant of, other anti-RA drugs. A dose-dependent response was observed in the American College of Rheumatology 20 (ACR20) response rates, with some evidence of dose-dependent toxicity. ACR20 response to monotherapy (3 mg/day) was lower than anti-tumour necrosis factor (TNF) therapies and in the same range as ciclosporin (cyclosporine) monotherapy.

Ciclosporin monotherapy may not fully control disease activity in all patients, with radiological progression slowly continuing.[1] This may also be the case with tacrolimus. Based on a single, open-label, noncontrolled trial, tacrolimus produced its best ACR20 response rate in combination with methotrexate. Methotrexate and tacrolimus have different mechanisms of action and toxicity patterns, possibly offering complementary efficacy at lower dosage. Tacrolimus combination therapy may represent a real option prior to patients being treated with TNF-antagonists.

Low-dose tacrolimus appears generally safe and well tolerated with slightly more serious adverse effects than placebo. Hypertension and nephrotoxicity are of particular importance. Low dosage and strict application to safety guidelines helps limit ciclosporin nephrotoxicity in RA.[1] Infection and malignancy also need to be considered. Mortality with tacrolimus in patients with RA needs to be studied in the longer term.

Longer term, double-blind, controlled trials that compare the efficacy and tolerability of tacrolimus with ciclosporin or other disease-modifying antirheumatic drugs (DMARDs) are now required. It is likely that tacrolimus has a narrow therapeutic window in patients with RA. Concentration targeting may further improve outcome.

Tacrolimus appears to be a realistic option in the treatment of patients with active RA. It may be most attractive when used in combination DMARD therapeutic strategies. ▲

Reference

1. Gremese E, Ferraccioli GF. Benefit/risk of cyclosporine in rheumatoid arthritis. Clin Exp Rheumatol 2004; 22 Suppl. 35: S101-7