The rationale for FK 506 in inflammatory bowel disease

JAMES C REYNOLDS, MD, DAN R TRELLIS, MD, KAREEM ABU-ELMAGD, MD, JOHN FUNG, MD

FK 506 is a novel macrolide immunosuppressant which is more potent than cyclosporine. Recent evidence that cyclosporine has efficacy in the treatment of inflammatory bowel disease (IBD) led to the development of a new protocol using FK 506. FK 506 has been shown to produce substantially greater survival in liver transplant patients than cyclosporine, with fewer side effects. Inhibition of lymphocyte production of cytokines interleukin (IL)-2, IL-3 and interferon gamma requires 10 to 100 times greater concentrations of cyclosporine than of FK 506. Rejection episodes are less frequent and side effects fewer in patients receiving heart, kidney or liver transplants following treatment with FK 506 than with cyclosporine. Thus, the development of a new, potent immunosuppressive agent with a greater safety profile than cyclosporine provides a new opportunity to identify an effective therapy for patients with IBD resistant to corticosteroids.

Key Words: Cyclosporine, FK 506, Immunosuppressant, Inflammatory bowel disease, Interleukins, Macrolide

W HILE THE INCITING EVENTS THAT initiate the activity in inflammatory bowel disease (IBD) remain an enigma, an over-activated immune response plays a major role in both Crohn's disease and ulcerative colitis (1). Medical therapy, therefore, has been aimed at modulating this aggressive immune response. The cornerstones of medical therapy for IBD include both sulphasalazine (and its derivatives) and corticosteroids. Typically, use of these agents will successfully manage 85 to 90% of patients with IBD. In addition to the 10 to 15% who do not respond to conventional therapy, another group of patients will experience adverse effects from long term corticosteroid treatment. These undesirable effects include mood changes, hypertension, glucose intolerance, osteoporosis, septic necrosis and cataracts.

Other immunosuppressives that have had success in treating other 'auto-immune' diseases have therefore been investigated to treat patients with IBD who are refractory to or intolerant of corticosteroids. 6-Mercaptopurine (6-MP) and azathioprine have proven efficacy in patients with refractory IBD (2,3). Unfortunately, these agents frequently require three months of therapy before demonstrating a response and while effective in 60 to 70% of patients with refractory IBD, 30 to 40% of patients with active disease do not respond.

Methotrexate has shown early promise in treating patients with re-
FK 506 is a newer agent (discovered in 1984) that is currently being investigated in organ transplantation. FK 506 is a macrolide antibiotic derived from Streptomyces tsukubaensis, a microorganism found in soil. Although structurally different from cyclosporine, the mode of action of FK 506 is similar to cyclosporine; it also acts by inhibiting the production of T lymphocyte cytokines but through different binding proteins. FK 506 in vitro is approximately 100 times more potent than cyclosporine in inhibiting the induction of T lymphocyte proliferation (9). FK 506 is more effective than cyclosporine in preventing rejection in liver, cardiac and renal transplantation and in improving patient and graft survival (10-12). Transplant patients with chronic rejection of the transplanted organ while taking cyclosporine have been salvaged when switched to FK 506. FK 506 is also more reliably absorbed than cyclosporine when ingested orally since it does not require the presence of bile (13). Although its toxicities are very similar to those of cyclosporine, FK 506 causes a lower incidence of hypertension (14).

Since cyclosporine appears to be effective in the therapy of refractory Crohn's disease and in refractory fulminant ulcerative colitis, it is possible that a medication that blocks the immune response at the same location, yet is more potent and has fewer adverse effects, may have a role in treating patients with refractory IBD. Because of this rationale, we have begun a three-month pilot study to investigate the efficacy and safety of FK 506 in patients with IBD who are refractory to or intolerant of corticosteroids.

FK 506 STUDY OUTLINE

The specific aims of this study are to: identify the lowest dose of FK 506 that exerts a beneficial effect on active IBD; determine the safety of FK 506 in patients with IBD; and determine whether FK 506 improves objective measures of disease activity including laboratory, endoscopic and radiographic findings, as well as improving symptoms. Patients were enrolled in this study if they had active IBD for longer than six months that had been inadequately controlled by corticosteroids, or if they had active IBD and were intolerant of corticosteroids. Crohn's disease is being studied separately from ulcerative colitis because these disorders differ with respect to the symptoms, complications and frequency of extraintestinal manifestations. This has led previous investigators to establish distinctive indices of disease activity. Standard definitions of these disorders will be used as defined in the inclusion and exclusion criteria. Early results are promising that these goals will be met. Several patients being treated for pyoderma gangrenosum had resolution of symptoms of Crohn's disease.

Chronic fistula drainage, unresponsive to all other medications, closed in response to FK 506. FK 506 has been well tolerated, and renal toxicity can be avoided by dose adjustment. The preliminary investigation indicates the need for further studies on the efficacy of FK 506 in the treatment of IBD.

REFERENCES


randomized trial of primary liver transplantation under immunosuppression with FK 506 vs cyclosporine. Transplant Proc 1991;23:2977-83


