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Tacrolimus: A Potential New Treatment for Autoimmune Chronic Active Hepatitis: Results of an Open-Label Preliminary Trial

David H. Van Thiel, M.D., **Harlan Wright, M.D.**, **Patricia Carroll, M.D.**, **Kareem Abu-Elmagd, M.D.**, **Horacio Rodriguez-Rilo, M.D.**, **John McMichael, B.Sc**, **William Irish, M.Sc**, and **Thomas E. Starzl, M.D., Ph.D.**
Pittsburgh Transplantation Institute, Section of Transplantation Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Abstract

Autoimmune chronic active hepatitis (CAH-A) is a chronic liver disease of unknown etiology that is believed to have an autoimmune pathogenesis. The disease is slowly progressive until hepatic failure and portal hypertension develop and either death or liver transplantation occur. Currently, the only widely recognized therapy is the administration of glucocorticoids, which have both anti-inflammatory and immunosuppressive actions. Many patients cannot tolerate such therapy because of the psychiatric, osteoporotic, and weight-enhancing actions of steroids. Tacrolimus (FK 506) is a new macrolide antibiotic that has an immunosuppressive activity that is estimated to be 10–200 times greater than that of cyclosporine. Because of its greater immunosuppressive activity, we have used it in the treatment of 21 patients with autoimmune chronic active hepatitis. Before each subject was treated, a liver biopsy and a panel of hematological, serological, and biochemical parameters were assessed. The Tacrolimus was administered orally at 12-h intervals, and the dose was controlled by monitoring plasma FK trough levels. After 3 months of therapy at an oral dose of 3 mg twice a day, having achieved a median blood level of 0.5 ng/ml, the serum ALT level was reduced by 80%, and the AST level was reduced by 70%. Modest change in the white blood cell count and platelet count were noted. The median BUN level increased from a level of 12 to 18 mg/dl, and the serum creatinine increased from 0.9 to 1.3 mg/dl. These preliminary data demonstrate that: 1) Tacrolimus can be used to successfully treat CAH-A; 2) the response of CAH-A to Tacrolimus treatment is rapid and sustained; and 3) a minor increase in the serum BUN and creatinine levels occurs as a consequence of Tacrolimus treatment. It is anticipated that with continued treatment for periods of 1–2 yr, the natural history of CAH-A will be changed such that hepatic failure and the requirement for liver transplantation may be averted.

INTRODUCTION

Autoimmune chronic active hepatitis (CAH-A) is a chronic disorder of the liver characterized by hepatocellular injury and the development of a mixed macro-micronodular cirrhosis associated with the presence of a variety of autoimmune serological markers, including any combination of the following: antinuclear antibody (ANA), anti-smooth muscle (ASM), anti-thyroglobulin (AT) and liver or kidney microsomal (LKM) autoantibodies, a polyclonal gammopathy, human histocompatibility leukocyte antigens (HLA) and antigens B8 and Dr3 (1–19). The disease can occur in individuals of either gender but is four times more common in women than in men and can clinically present

Reprint requests and correspondence: David H. Van Thiel, M.D., Oklahoma Transplant Institute, Baptist Medical Center of Oklahoma, 3300 Northwest Expressway, Oklahoma City, OK 73112.

either as a chronic hepatitis with or without cirrhosis in the teenage years or as an established cirrhosis in an adult patient (1–6).

The specific etiology of CAH-A is unknown, but its association with HLA antigens B8 and Dr3 and a panoply of autoantibodies suggest that it is a consequence of an abnormal immune response directed at liver cells in response to a common viral agent or other environmental factor (9–21). Because of its presumed autoimmune etiology, a variety of immunosuppressive agents have been used in its clinical management (22–32). These include glucocorticoids, methotrexate, azathioprine, cyclophosphamide, d-penicillamine, cyclosporin A, and, in the present preliminary report, Tacrolimus (FK 506). The use of Tacrolimus for patients with CAH-A has not been reported previously.

METHODS

Subjects

A total of 21 subjects with a histological and serologically confirmed diagnosis of CAH-A were studied. Each subject had a liver biopsy consistent with the diagnosis (7,8) and had one or more autoantibodies known to be associated with CAH-A. In addition, five were HLA B8-positive, and six were Dr3-positive. All subjects gave their informed, written consent for their participation in this study. Moreover, this study was approved by the committee evaluating human studies at the University of Pittsburgh before its initiation.

Pretherapy evaluation

Each subject underwent a thorough pretherapy evaluation that included the following studies:

1. Complete blood count with platelet count;
2. A panel of liver injury and function parameters to include total bilirubin, ALT, AST, alkaline phosphatase (alk phos), γ glutamyl transpeptidase (GGPT), a serum electrophoresis, and a prothrombin time;
3. A percutaneous liver biopsy for histological evaluation and quantitation of the hepatic iron and copper content;
4. A CT scan of the liver for determination of liver volume;
5. An ultrasound examination of the liver to determine the status of the liver, biliary tree, and portal and hepatic vessels;
6. A panel of autoantibodies to include ANA, ASM, AT, and LKM.

Patient monitoring

After the pretherapy evaluation procedures were completed, each subject was given Tacrolimus at a starting dose of 0.075 mg/kg taken orally as equally divided doses 12 h apart. The initial dose was increased or reduced at 2-wk intervals to achieve a trough serum Tacrolimus level of 0,6–1.0 ng/ml. All Tacrolimus serum levels were obtained after an overnight fast and before the next morning's dose (33). Initially, all subjects were seen weekly (approximately 4 visits), then bi-weekly (2–3 visits), then monthly (2–3 visits), and finally, quarterly, until a 1-yr study period was completed.

At each visit, the following studies were obtained: 1) Complete blood count with platelet count; 2) Electrolytes, BUN, creatinine, blood sugar; 3) A liver injury panel consisting of the serum bilirubin, ALT, AST, alk phos, and γGTP levels; 4) A serum tacrolimus level. At the end of a full year on the drug, all of the studies performed as part of the prestudy evaluation

were repeated. All liver biopsies were read by staff pathologists at the University of Pittsburgh who were blinded to the nature of this study and the timing of the biopsies.

Statistical analysis

All results are presented as mean valued SEM.± All data were compared using the entry and exit pleasures. The Student's one-tailed t test was used for statistical analysis. A p value <0.05 was considered significant.

RESULTS

A total of 21 subjects were enrolled in the open-label preliminary study evaluating the efficacy and toxicity of Tacrolimus in the treatment of CAH-A, The demographic data available on these 21 patients are shown in Table 1. As expected, most patients were women. More than half had one or another marker of an abnormal immune response (autoantibody) and were positive for the HLA antigens B8, Dr3, and DrBW52. The clinical characteristics of these same patients are shown in Table 2. Most had clinical jaundice, and all had markedly elevated ALT and AST levels. The patients hematological parameters and renal function measures were normal. The time to achieve a stable serum Tacrolimus level between 0.6 and 1.0 ng/ml and to maintain renal function at acceptable levels was 3.0 ± 0.5 wk. The mean Tacrolimus dose prescribed on a daily basis at this plateau level was 7.2 ± 0.8 mg/day, and the mean daily dose on a per kg basis was 0.06 ± 0.01 mg/kg/day.

As a result of the Tacrolimus treatment, the ALT and AST levels fell dramatically, as shown in Figure 1. Similarly, the serum total bilirubin level declined to a normal value (Fig. 2). The alkaline phosphatase level declined also but to a lesser degree and less consistently, probably because of the high rate of established cirrhosis in the populations studied (Fig. 2 and Table 1). The changes in the white blood cell counts and the platelet counts observed with Tacrolimus therapy are shown in Figure 3. The minor increase in BUN and creatinine observed with Tacrolimus therapy is shown in Figure 4.

DISCUSSION

CAH-A is a chronic hepatitis characterized histologically as showing piecemeal necrosis with a mononuclear infiltrate that consists predominantly of plasma cells and lymphocytes (1–8). Pathophysiologically, the disease is thought to represent an example of antibody-dependant cellular cytotoxicity mediated predominantly by natural killer cells (34–40). Individuals with this disease are thought to have an underlying genetic defect that makes them susceptible to an abnormal immune response to an environmental agent, either a virus (measles, cytomegalo virus or other) and to develop antibodies directed at a cross-reacting antigen or liver cells that enable natural killer cells to attack and kill antibody-coated hepatocytes (9–21).

In most studies, the serum AST and the degree of histological activity have been shown to be related (7,8). This relationship between the serum AST level and the severity of the histological disease process is most apparent early in the disease course and is less strong as the disease progresses to cirrhosis and, ultimately, decompensated cirrhosis. Moreover, the histological disease is the parameter of disease severity that requires the longest time to correct with therapy, occurring weeks to months after clinical and biochemical resolution of disease (22,30). Even with excellent clinical (subjective) and biochemical evidence for disease remission, half of the patients, when biopsied after 2 yr of glucocorticoid therapy either alone or in combination with azathioprine, will show continued disease activity. These latter patients are generally continued on immunosuppressive therapy lifelong (41–44).

Because of concerns about lifelong treatment of patients, the majority of whom are women and are, as a result, susceptible to enhanced rates of osteoporosis with glucocorticoids, some patient with CAH-A have been treated with cyclosporine A (CyA) (31). This latter agent is a more specific T cell specific immunosuppressive agent and has been used because of its powerful inhibitory effects on $CD4^+$ lymphocytes. Specifically, CyA reduces interleukin-2 (IL-2) production and IL-2 receptor expression on T lymphocytes and powerfully suppresses overall immune reactivity, presumably including that due to antibody-dependent cellular cytotoxicity, which is thought to be the mechanism responsible for liver cell injury and death in CAH-A. Preliminary trials with CyA have been promising but have been limited by the nephrotoxicity associated with its use (31).

Tacrolimus is a new macrolide antibiotic with immunosuppressive activity that is reported to be 100–1000 times more powerful on a molecular basis than CyA when treated in various *in vitro* assay systems (45). Clinically, Tacrolimus has been shown to be useful in organ allograft recipients when CyA either has not worked or its use has been limited by nephrotoxicity or some other manifestation of drug toxicity, such as hypertension or neurotoxicity (46–53).

The present study was initiated to determine whether or not Tacrolimus could be used in cases of CAH-A to obtain control of the disease process and if so, at what cost in terms of its nephrotoxicity, neurotoxicity, and diabetogenic activity? As is readily apparent from the data presented in Figures 1–4, Tacrolimus can be used effectively to treat CAH-A. Moreover, the cost of such treatment in terms of the nephrotoxicity of chronic Tacrolimus administration at the doses and levels used in this study are not particularly severe (Fig. 4) and therefore not limiting. Specifically, a greater than 75% reduction in ongoing hepatic injury as manifested by the serum levels of AST and ALT was noted with Tacrolimus therapy (Fig. 1). Moreover, a substantial improvement in hepatic function, as manifested by the decline to normal of the serum bilirubin level, was observed with continued Tacrolimus treatment (Fig. 2).

The change in renal function observed as a result of Tacrolimus treatment was minor and at no time limited therapy (Fig. 4).

These results suggest that Tacrolimus should be used in a randomized control study against prednisone to define its clinical efficacy against the best available current therapy.

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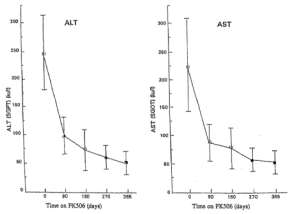

Fig. 1.

Serum ALT and AST levels at entry and 3-month intervals after slarting Tacrolimus therapy. The *points* represent mean values; the *brackets* represent the SEM.

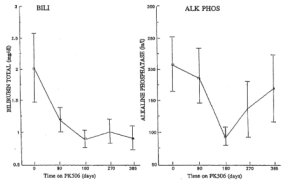

Fig. 2.

Serum bilirubin and alkaline phosphatase levels at entry and at 3-month intervals while on Tacrolimus. The points represent mean values; the brackets represent the SEM.

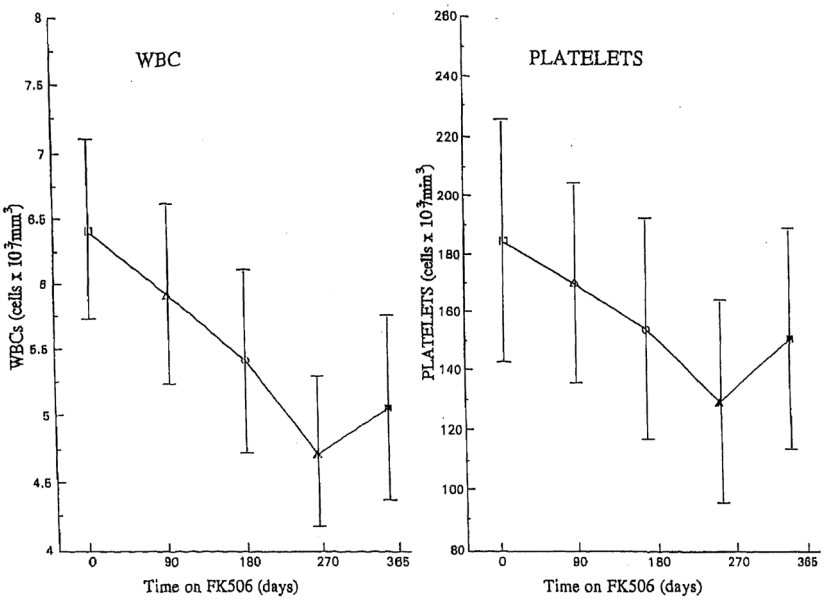

Fig. 3.

White blood cell and platelet counts in patients with CAH-A while receiving Tacrolimus. The *points* represent mean values; the *brackets* represent the SEM.

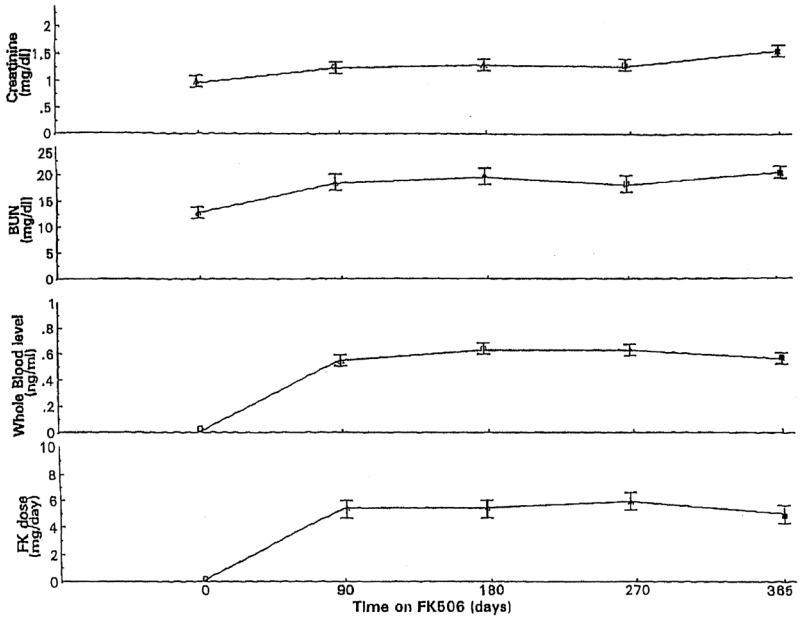

Fig. 4.

Serum creatinine and BUN levels in the patients treated with Tacrolimus for CAH-A. The dose and blood level of Tacrolimus achieved is also shown. The *points* represent mean values; the *brackets* represent the SEM.

Table 1

Demographic Data on the Subjects Studied

Parameter	Result
Gender (Male/Female)	17/4
Age (Years)	42.3 ± 3.7
Duration of disease (Years)	4,2 ± 0.7
CAH alone at entry	52%
CAH + cirrhosis at entry	48%
Liver volume (cc)	1335 ± 119
HLA B8 positive	50%
HIA Dr3 positive	50%
HIA DrBW52 positive	72%
ANA positive	100%
Anti-smooth muscle positive	35%
Anti LKM positive	50%

Table 2

Initial Clinical Characteristics of the Patients Studied.

Parameter	Result	Normal
Total Bilirubin (mg/dl)	2.0 ± 0.7	<1.2
AST (IU/ℓ)	224 ± 97	<32
ALT(IU/ℓ)	248 ± 81	<32
Alkaline Phosphatase (U/ℓ)	210 ± 41	<125
WBC ($\times 10^3$)	5.1 ± 0.8	5–10
Platelet ($\times 10^3$)	185 ± 49	150–300
BUN (mg/dl)	12.6 ± 1.9	5–20
Creatinine (mg/dl)	0.9 ± 0.1	<1.2