

# FK 506 Rescue in Chronic Graft-Versus-Host-Disease After Bone Marrow Transplantation

A.G. Tzakis, K. Abu-Elmagd, J.J. Fung, E.J. Bloom, B. Nour, F. Greif, and T.E. Starzl

**C**HRONIC graft-versus-host-disease (GVHD) is a debilitating and often fatal complication seen in 30% to 60% of patients undergoing allogeneic bone marrow transplantation (BMT).<sup>1</sup> Its prognosis is poorer with advancing patient age, when it is extensive, if it appears progressively after acute GVHD, if total bilirubin is more than 1.2 mg/dL, or if the platelet count is less than 100,000/mL. Conventional treatment includes combination immunosuppression most often with cyclosporine (CyA) and prednisone. Azathioprine, methotrexate, antilymphocyte globulin, and other therapies may also be used.<sup>1-6</sup>

FK 506 is a potent new immunosuppressive agent effective in rescue of solid organ transplant patients who failed conventional treatment for immunologically mediated damage.<sup>7</sup>

We attempted rescue of patients with severe chronic GVHD after BMT who had failed conventional treatment.

### INCLUSION CRITERIA

Patients were accepted into the study if they had extensive chronic GVHD after failure of at least 2 months of first-line therapy. Alternatively, patients were entered if they demonstrated unchanged symptomatology after 9 months of treatment, or had severe adverse reactions from drugs used in first-line treatment.

### EXCLUSIONS

Three patients with severe chronic GVHD were not accepted for FK 506 treatment: 1 had coexistent necrotizing pancreatitis and 2 had aspergillus pneumonia. All 3 patients died from these complications within 2 weeks of referral. Three BMT patients received FK 506 for indications other than chronic GVHD (acute GVHD, *n* = 1; veno-occlusive disease, *n* = 2) and are not included here. The first patient died of disseminated aspergillosis 3 days after FK 506 treatment was initiated. The latter 2 patients died of pulmonary complications after liver transplantation.

### TREATMENT PROTOCOL

Initial FK 506 dose was 0.15 mg/kg BID orally or 0.15 mg/kg per day IV. The dose was adjusted upward until a clinical response was seen, or at least to maintain a blood level between 1 and 2 ng/mL. The dose was lowered if a clinically significant side effect occurred; most commonly the dose was lowered when there was evidence of progressive nephrotoxicity.

Corticosteroids were tapered to the lowest possible dose necessary to maintain clinical response.

CyA and all other immunosuppressive agents, except steroids, were discontinued 24 to 48 hours prior to administration of FK 506.

All patients received trimethoprim-sulfamethoxazole prophylaxis (one double-strength tablet PO BID twice weekly for adults or an equivalent dose for children).

### RESULTS

Seventeen patients entered the study; their clinical profile is shown in Table 1. The preparative regimen, GVHD prophylaxis, and treatment received for chronic GVHD prior to entry into the study varied and are shown in Table 2.

All patients received CyA for GVHD prophylaxis and treatment of chronic GVHD most often in combination with prednisone and other immunosuppressive agents. The time elapsed between BMT and FK 506 treatment varied from 5 to 55 months (mean 21.4 months). Chronic GVHD developed de novo in one patient, was of the quiescent type in seven patients and of the progressive type in nine patients. Organs affected included liver, lungs,

Table 1. Clinical Profile (N = 17, All Patients)

Age
Children 4-12 years (mean = 8.7) = 5 patients
Adults 16-47 years (mean = 34.5) = 12 patients
Sex
Male/Female: 12/5
Diagnosis
Chronic myeloid leukemia: 7
Acute lymphoid leukemia: 4
Acute myeloid leukemia: 2
Aplastic anemia: 2
Burkitt's lymphoma: 1
San Filippo syndrome: 1
HLA matching
Identical: 13*
Nonidentical: 4

\*One graft was from a nonrelated donor.

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania.

Supported by research grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, Maryland.

Address reprint requests to Thomas E. Starzl, MD, PhD, Department of Surgery, 3601 Fifth Avenue, University of Pittsburgh, Pittsburgh, PA 15213.

© 1991 by Appleton & Lange  
0041-1345/91/\$3.00/+0

**Table 2. Treatment Received Before FK 506 Rescue**

Preparative regimen:
Variable: Cyclophosphamide, busulfan, TBI
GVHD prophylaxis:
CyA + prednisone: 8
CyA + methotrexate: 3
CyA + prednisone + azathioprine: 4
CyA + prednisone + methotrexate: 1
CyA + methotrexate followed by CyA + prednisone + azathioprine: 1
Chronic GVHD treatment:
All patients received CyA + prednisone
Other agents used: azathioprine (7), ATG (2), xomazyme (2), PUVA (1)

gastrointestinal tract, skin, musculoskeletal, and oral mucosa. It involved two organs in four patients, three organs in five patients, four organs in four patients, five organs in three patients, and six organs in one patient. Nine patients had total serum bilirubin greater than 1.2 mg/dL, 10 exhibited lichenoid skin histology, seven patients had lung involvement, and one patient had a platelet count of less than 100,000/mL.

#### Patient Survival

Currently, 11 of the patients are alive and 6 are dead with a follow-up period of 3 to 16 months (mean 8.4 months). Two patients required liver transplantation after starting FK 506 treatment. One of them is alive and well 3 months following the procedure, and the second died of respiratory distress syndrome and multiorgan failure 8 weeks after transplantation. The results are summarized in Tables 3 and 4.

#### Response According to Systems Involved

The organ systems involved demonstrated different response to treatment independent of the patient's survival.

**Table 3.**

Results (all patients): 11 alive\*, 6 dead†

#### Survival according to age

Children: 4 alive, 1 dead  
Adults: 7 alive, 5 dead

#### Survival according to system involved (all patients):

Skin: 7 alive, 6 dead  
GI: 6 alive, 4 dead  
Lungs: 3 alive, 4 dead  
Musculoskeletal: 3 alive, 2 dead

#### Survival according to type of onset (all patients):

De novo: 1 alive, 0 dead  
Quiescent: 4 alive, 3 dead  
Progressive: 6 alive, 3 dead

\*Including 1 child who is alive after liver transplantation.

†Including 1 adult who died after liver transplantation. Follow-up: 3–16 months (mean 8.4 months).

**Table 4. Clinical Response to Treatment (Survivors N = 11)**

Unambiguous improvement: 6 patients
Ambiguous improvement or unchanged: 2 patients
Stopped FK 506: 2 patients
Alive after liver transplantation: 1 patient

The skin and GI system showed unambiguous improvement. Follow-up GI biopsies were performed in two children, and both demonstrated disappearance of GVHD which was present in both at rescue.

Musculoskeletal involvement showed no response to treatment. Lung involvement showed no change in four and deterioration in three patients, confirmed by pulmonary function tests.

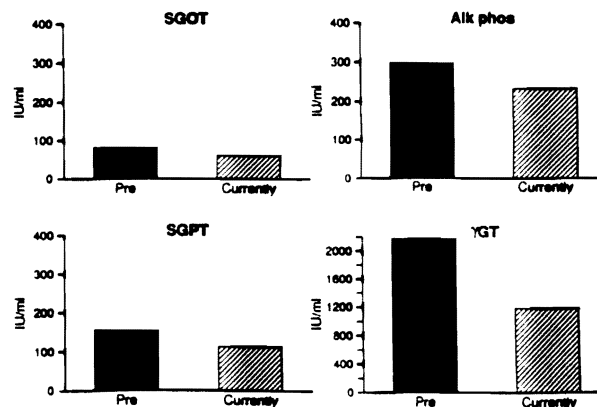
Of the survivors, two patients who did not improve on FK 506 were converted to their original CyA regimen. One patient is well after liver transplantation on FK 506 treatment. Of the remaining eight patients, six showed unambiguous improvement, while two showed minor improvement or remained unchanged and are still on FK 506.

#### Liver Involvement

The mean values of the liver enzymes at entry and at follow-up in patients who are alive with their native liver ( $n = 8$ ) are shown in Fig 1. Fig 2 shows the changes of the mean total serum bilirubin of these patients. All of the patients had improvement. Four children had liver biopsies at 3 months and 6 months after FK 506 treatment was instituted. Despite clinical and biochemical improvements, there was no appreciable histological change as compared to pretreatment biopsies.

#### Steroid Requirements

Fig 3 shows the mean prednisone (prednisolone) dosage of these patients during follow-up. One of the children, as well as the child who received the liver transplant, are currently receiving no steroids.

**Fig 1.**

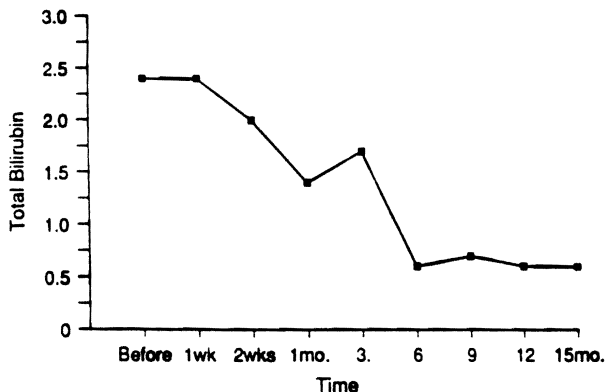


Fig 2. Total bilirubin (survivors—native liver with liver affect) (N = 8).

#### Complications

An elevated serum creatinine level was common after conversion to FK 506 and decreased over time. Two patients currently have a serum creatinine of >2 mg/dL (2.4 mg/dL at 3 months after rescue, 2.2 mg/dL at 6 months after rescue). Two additional patients required dialysis in the treatment of multiorgan failure pre-mortem.

Eight patients are receiving treatment for hypertension, four of them were receiving such treatment before treatment with FK 506. No patients developed diabetes mellitus or seizures. To the contrary, one patient who had repeated seizures on IV CyA did not have any seizure activity on FK 506.

Infections while under treatment with FK 506 are shown in Table 4. Of those, three were fatal.

There was no loss of bone marrow graft or development of malignancies (recurrent or de novo) under FK 506 therapy.

#### DISCUSSION

FK 506 rescue in chronic GVHD after BMT was attempted because of the potency of FK 506 and its known ability to

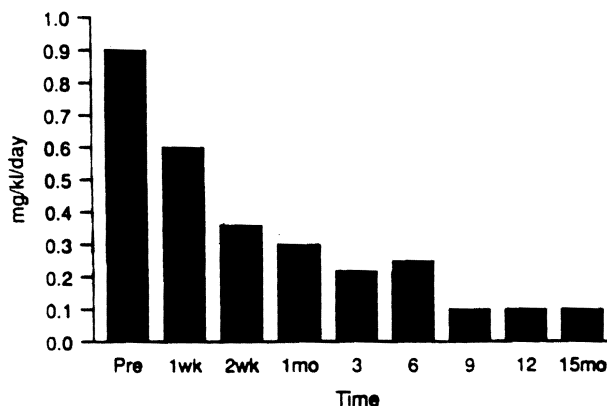


Fig 3. Dose of prednisone (survivors).

Table 5. Infections in FK 506 Rescue for Chronic GVHD

Bacterial
3 Broviac catheter sepsis
1 Streptococcal pneumonia
Viral
1 Viral pneumonia*
Fungal
2 Aspergillosis*
1 Candida UTI

\*Fatal infection.

rescue solid organ allografts, particularly livers, undergoing chronic rejection even after failure of conventional therapy.<sup>7</sup> Of the 17 patients reported here, 6 had a beneficial response to FK 506 treatment, achieved with relative freedom from steroids.

Nephrotoxicity was the most common side effect of FK 506 treatment. It was consistently more severe soon after rescue and then tended to decrease with time and dose reduction. A similar effect has been seen in rescue of solid organ recipients and is thought to be, at least in part, an overlapping effect from FK 506 and CyA.<sup>7</sup>

The increase in the number of patients receiving treatment for hypertension is different than the experience with FK 506 for solid organ transplantation.<sup>8</sup>

An inherent difficulty of this study is the quantitative evaluation of the results, because of the variety of clinical presentations in the spectrum of chronic GVHD.

The correction of abnormal liver function studies, provided an objective monitor of the response to treatment. The lack of histopathologic improvement in the available liver biopsies could be due to the subtlety of both pathology and effect of FK treatment. Indeed, pathologic changes may require longer periods of time to resolve.

Patients with pulmonary and musculoskeletal involvement have, as yet, failed to improve with FK 506 treatment.

This pilot series suggests that FK 506 can be of help when conventional treatment has failed in the treatment of chronic GVHD following BMT. It is possible that the apparent advantage is also evident if FK 506 is used earlier in the course of GVHD.

#### REFERENCES

- Sullivan KM, Shulman HM, Storb R, et al: *Blood* 57:267, 1981
- Sullivan KM, Witherspoon RP, Storb R, et al: *Transplant Proc* 20:555, 1988
- Sullivan KM, Siadak MR, Witherspoon RP: *Transplant Proc* 22:1336, 1990
- Wingard JR, Piantadosi S, Vogelsang GB, et al: *Blood* 74:1428, 1989
- Vogelsang GB, Santos GW, Colvin OM, et al: *Lancet* i:827, 1988
- Ferrara JLM, Deeg HJ: *New Engl J Med* 324:667, 1991
- Fung J, Todo S, Tzakis A, et al: *Transplant Proc* 23:14, 1991
- Shapiro R, Fung JJ, Jain A, et al: *Transplant Proc* 22:35, 1990