# Letters to the Editor

## TREATMENT OF CYCLOSPORIN-INDUCED HAEMOLYTIC URAEMIC SYNDROME WITH FK506

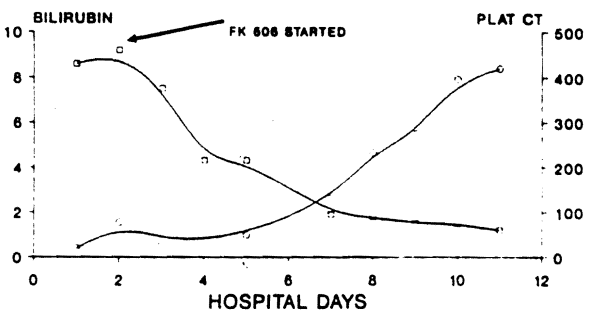
SIR,—Haemolytic uraemic syndrome (HUS) is a well-recognised complication of cyclosporin therapy in organ transplantation.[1-4] It has usually been treated by a switch to azathioprine. We report the first use of FK506 in the management of this complication. A 33-year-old man had liver transplantation in January, 1989, for end-stage liver disease due to chronic active hepatitis. Recovery was complicated by acute tubular necrosis which required haemodialysis for 3 weeks. He was discharged 7 weeks postoperatively with normal liver function, normal haematological profile, serum creatinine 2·4 mg/dl, and blood urea nitrogen (BUN) 24 mg/dl. His daily medications were cyclosporin 600 mg, azathioprine 75 mg, acyclovir 200 mg, and trimethoprim 80 mg plus sulphamethoxazole 400 mg.

7 months postoperatively, he became anaemic with a haematocrit of 14·7%, platelet count of 29 000/μl, and white cell count 5800/μl. Total bilirubin rose to 5·7 mg/dl, creatinine to 5·0 mg/dl, and BUN to 69 mg/dl. His cyclosporin level, which was therapeutic, was 713 ng/ml (TDX method). A blood smear revealed microangiopathic haemolytic anaemia. The urine contained trace protein and the sediment had 1-3 hyaline casts per high-power field. The patient was afebrile and without major complaints. Because of the microangiopathic haemolytic anaemia, thrombocytopenia, and renal failure, cyclosporin-induced HUS was diagnosed.

When the platelet count and haematocrit continued to fall for 2 days after admission, azathioprine and cyclosporin were discontinued. FK506 was started at 8 mg daily (0·15 mg/kg) intravenously and changed to 16 mg per day orally after 3 days. Within 24 h of the start of FK506 the platelet count had increased to 130 000/μl, and by the seventh day it was 420 000/μl (figure). The haematocrit rose progressively, starting on day 6. Renal function initially worsened but also began to improve on day 7 of FK506 therapy. Dialysis was not required. Total bilirubin fell promptly (figure). The patient was discharged after a week, and a week after this his serum creatinine was 4·2 mg/dl and platelet count 420 000/μl.

After discharge, the dose of FK506 was arbitrarily halved. 4 weeks later HUS abruptly recurred with thrombocytopenia, hyperbilirubinaemia, and acute renal failure. The oral FK506 dose was restored to 16 mg daily, with resolution of the HUS within a few days and during the ensuing 6 weeks.

This patient quickly recovered from cyclosporin-induced HUS without the need for plasmapheresis or other ancillary therapy. Cyclopsorin-induced HUS is often fatal[1-4] and poor control of graft rejection accompanies the discontinuation of cyclosporin. In our patient the offending immunosuppressive agent was replaced by a more potent one.[5] Cyclosporin and FK506 both inhibit interleukin-2 production and binding and selectively suppress T-cell function. However, the two drugs have a completely different chemical structure, and this may explain the salutary effects of FK506 in cyclosporin-induced HUS.




**Hospital course of patient with cyclosporin-induced HUS.**

PLAT CT (○——○) = platelet count (1000s/μl) and BIL1 (□——□) = serum bilirubin (mg/dl).

Rapid recovery, as seen in this case, has been uncommon. Gradual improvement of the haematological picture has been the usual course as cyclosporin is cleared from the plasma with or without plasmapheresis. Cyclosporin-induced endothelial cell injury is the probable proximate event in the pathogenesis of HUS in most cases. However, autoimmune haemolytic anaemia has also been described.[6,7] The ancillary manoeuvres used to treat cyclosporin-induced HUS are directed at immune mechanisms. FK506, the most potent immunosuppressant yet used clinically,[5,8] may exert its effect not only by substituting for cyclosporin but also by treating the primary immunological origin of this disorder.

Supported by grants from Veterans Administration and National Institutes of Health (DK 29961).

Departments of Surgery and Medicine, University Health Center of Pittsburgh, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA; and VA Medical Center, Pittsburgh

JERRY MCCAULEY
OSCAR BRONSTHER
JOHN FUNG
SATORU TODO
THOMAS E. STARZL

1. Akinson K, Biggs JC, Hayes J, Ralston M, Dodds AJ, Concannon Naidoo D. Cyclosporin A associated nephopathy in the first 100 days after allogeneic bone marrow transplantation: three distinct syndromes. *Br J Haematol* 1983; 54: 59–67.
2. Van Buran D, Van Buran CT, Flechner SM, Maddox AM, Verani R, Kahan BD. De novo hemolytic uremic syndrome in renal transplant recipients immunosuppressed with cyclosporine. *Surgery* 1985; 98: 54–62.
3. Faure JL, Causse X, Bergeret A, Meyer F, Neidecker J, Paliard P. Cyclosporine induced hemolytic anemia in a liver transplant patient. *Transplant Proc* 1989; 21: 2242–43.
4. Goldman MH, Barnhart G, Monanankumar T, et al. Cyclosporine in cardiac transplantation. *Surg Clin N Am* 1985; 65: 637–59.
5. Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramanan R, Jain A. FK 506 for liver, kidney, and pancreas transplantation. *Lancet* 1989; ii: 1000–04.
6. Zola C, Furci L, Ghilardi F, Zilio P, Benigni A, Remuzzi G. Cyclosporine-induced endothelial cell injury. *Lab Invest* 1986; 55: 455–62.
7. Schlanger RE, Henry ML, Sommer BJ, Ferguson RM. Identification and treatment of cyclosporine-associated allograft thrombosis. *Surgery* 1986; 100: 329–33.
8. Starzl TE, Makowka L, Todo S, eds. FK-506: a potential breakthrough in immunosuppression. *Transplant Proc* 1987; 19 (suppl 6): 3–104.

## CLINICAL TRIALS WITH ORAL IRON CHELATOR L1

SIR,—Your Oct 28 editorial (p 1016) states that trials with the oral iron chelator 1,2-dimethyl-3- hydroxypyrid-4-one (L1) should be suspended. A cheap, effective, and safe oral iron chelator is urgently needed, so we should examine carefully the evidence on which you base your advice to stop trials with a low-cost drug that has already been shown to be orally effective at removing iron.[1,2] You refer to the development of agranulocytosis in 1 patient, joint pains in 3 patients, 2 deaths of patients who received the drug, and leucopenia in rats and mice receiving subacute doses of L1.

At an international meeting in London (Nov 2–4, 1989), data on 120 patients who have received L1 for between 1 and 15 months were presented. Apart from our 1 patient with Blackfan-Diamond anaemia[3] no patient experienced a change in neutrophil, lymphocyte, or platelet count. Blackfan-Diamond anaemia is a condition in which neutropenia is well recognised: this single case does not argue for all trials to be abandoned though we would advise against the drug being given to other patients with the Blackfan-Diamond anaemia, at least for the time being.

Mild transient musculoskeletal aches were described in 3 of 24 thalassaemia major patients treated in Bombay, and we have noted this in 3 of our patients.[4] There is no direct evidence that these symptoms were drug induced and toxicity in the joints arising via iron complexes is unlikely to be correct since short-term clinical trials in rheumatoid arthritis patients in the Netherlands revealed no such toxicity.[5]

1 of the 2 patients who died[6] was a total non-complier with subcutaneous desferrioxamine with gross iron overload, congestive heart failure, cardiac arrhythmias, and diabetes who asked to be put on L1. The chelator was taken for 2 months, but had not been taken for 6 weeks before her death from infection and cardiac failure. Her white cell count had not changed. Many other non-compliers with desferrioxamine have had cardiac failure, and this may not be reversible even by intravenous desferrioxamine at high doses. The second patient to die, 5½ weeks after stopping L1, had progressive myelodysplasia with increasing blasts in the marrow, not a situation