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FK 506 Used as Rescue Therapy for Human Liver Allograft Recipients

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THE new immunosuppressant, FK 506, was first used in humans on a compassionate basis, for patients suffering from intractable rejection or disabling side effects of cyclosporine (CyA) therapy.[1-3] This report is a brief overview of a much larger experience with a longer follow-up, presented in detail elsewhere.[4]

PATIENTS AND METHODS

Patient Selection

The clinicopathologic profile of all liver allograft recipients who were converted from CyA–steroid to FK 506 therapy during the period of March 1, 1989 until December 15, 1989 was reviewed. Ninety-six of 136 patients identified were included in this study based on the following criteria: (1) biochemical graft dysfunction, as defined by elevated liver function tests (>50% over normal values) in the absence of mechanical causes; and (2) availability of a liver biopsy within 7 days before the switch, with at least one follow-up biopsy afterward.

All patients were followed until September 9, 1990, graft failure, or death, which ever came first. The results of liver function tests were recorded, 30, 60, 90, and 180 days after conversion.

Pathologic Studies

The diagnosis of acute and chronic liver allograft rejection was based on previously published criteria.[4,5]

RESULTS

The results of conversion to FK 506 were stratified according to the reason for conversion, based on the clinicopathologic profile of each patient prior to the switch. The results are summarized in Table 1. As can be seen, the majority of patients whose graft dysfunction was attributable to acute or the early stages of chronic rejection, while under conventional therapy, responded favorably to the conversion to FK 506. All but two of the 18 patients switched for acute rejection had received additional steroid (n = 12) and/or OKT3 (n = 7) before conversion.

Nonrejection causes of graft dysfunction were mostly unaffected pathologically by FK 506, except for acute or chronic active hepatitis, which proved to be a poor indication for conversion. Improvement of biochemical parameters of liver injury was more common than pathologic improvement in all categories. The discrepancy may have been due to discordance between the date of last biopsy and liver function test monitoring.

Transient FK 506 nephrotoxicity was often observed at the time of drug switch and was severe in some patients, although none required dialysis. However, for all patients taken as a group, there was no significant change in serum creatinine values 180 days after conversion to FK 506 (mean serum creatinine pre-FK 506 = 1.8 ± 0.9 mg/dL, post-FK 506 = 1.9 ± 0.9 mg/dL; $P > .05$).

DISCUSSION

The results of this analysis suggest that FK 506 is a more potent immunosuppressant than other current agents.

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Table 1. Summary of Clinicopathologic Profile of Patients Prior to Conversion and Outcome After Switch to FK 506, Based on at Least 9 Months Follow-Up

Pre–FK 506 Diagnosis	No. Patients	Died	Retransplanted	Functioning	Histologic Follow-Up			Biochemical Parameters of Liver Injury After Conversion[3]
					Improved	No Change	Worse	
Acute cellular rejection	18	3	1	14	10	4	0	Improved
Chronic rejection	33	0	11*	22†	13	9	0	Improved
Chronic rejection[4] CPH/CAH	20	0	4	16	1	10	5	Mixed
Hepatitis[5]	7	4	1	2	0	0	2	Worse
Nonspecific changes[1]	18	0	0	18	0	18	0	Same

*Seven/11 patients had >50% bile duct loss and total serum bilirubin >15 mg/dL prior to conversion.

†All but 2 patients had <50% bile duct loss and total serum bilirubin <15 mg/dL prior to conversion.

‡Initial cause of graft malfunction was uncertain. Difficulty in separating ongoing rejection from chronic persistent (CPH) or low-grade chronic active hepatitis (CAH) was encountered.

§Acute and chronic active.

‖Patients were switched primarily for reasons other than graft dysfunction.

¶Based on examination of functioning grafts 180 days after conversion.

However, it may be that conversion to a new immunosuppressant after the development of rejection can effectively control a clone of lymphocytes that was selected prior to the switch, because of its resistance to the original regimen.[5]

Regardless, the data generated from this study cannot be used for a comparison of FK 506 with continuation of conventional therapy, since the latter option was considered inhumane. A more direct comparison, as is now being conducted in the randomized European and American trials, should yield more definitive answers. Also, a comparison and quantification of the side effects will be achieved. The results reported herein for rescue patients place FK 506 in a favorable light. However, continued follow-up of these and other patients for potential chronic toxicity will place FK 506 in its proper perspective in the immunosuppressive arsenal.

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