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FK506 rescue therapy for intractable liver allograft rejection

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Abstract Intractable liver allograft rejection remains an important cause of graft loss. In this present study, we evaluated the role of oral FK506 in 30 rejection episodes resistant to conventional cyclosporin-based triple immunosuppression in a series of 28 patients. Rejection was reversed in 11 (91.7%) of 12 patients for intractable acute rejection and in 10 (58.8%) of 17 patients for chronic rejection. A progressive decline in serum bilirubin was observed within 14 days in those successfully salvaged and a serum bilirubin of less than 200 μmol/l at the time of FK506 conversion in the chronic rejection subgroup was found to be good predictor of response (specificity 100%, sensitivity 60%). New onset diabetes mellitus (29%) and reversible renal impairment (32%) were the commonest adverse events observed. Eleven (52%) of the responding patients successfully discontinued corticosteroid medication and are currently on FK506 monotherapy. FK506 therapy has a significant impact in the control of both intractable acute and chronic allograft rejection with an acceptable toxicity profile.

Key words Intractable rejection
FK506 · Liver transplantation

Introduction

Until recently, retransplantation was the only therapeutic option available for intractable rejection and one that was associated with a significantly increased morbidity and mortality. In 1989, Starzl and colleagues first reported the successful clinical use of FK506, a novel macrolide antibiotic with potent immunosuppressive activity, in the reversal of liver allograft rejection after failure of conventional immunosuppression [17, 12]. These promising early results have been confirmed in an expanded series from the Pittsburgh group detailing the clinicopathological findings of a group of 96 liver graft recipients converted from cyclosporin to FK506 [5]. In that report, patients with advanced chronic rejection had a less favourable outcome than did those patients converted early in the course of chronic rejection, or with acute rejection. Further uncontrolled studies have reported similar results, with graft salvage achieved in 65–95% for intractable acute rejection and in 50–70% of those with chronic rejection [4, 7, 8, 10, 11, 13, 20, 22]. There remains, however, a significant subgroup of patients in whom FK506 is not effective and accurate prognostic indices to identify these are required so that early retransplantation can be attempted. Analysis of data from the US multicenter FK506 Liver Study Group has revealed that increased serum levels of bilirubin and aspartate transaminase, but not preconversion liver his-

tology, independently correlate with treatment success [19].

In this present report, we analysed results of the King's College Hospital experience with FK 506 administered for the treatment of episodes of intractable acute and chronic rejection episodes.

Patients and methods

Between 1 January 1991 and 31 December 1992, 28 adult liver allograft recipients were converted to an FK 506-based immunosuppressive regime on account of 13 episodes of intractable acute rejection (IAR) in 12 patients (one patient received FK 506 for reversal of intractable acute rejection in two consecutive grafts) and 17 episodes of chronic rejection (CR). In two cases, IAR was precipitated by self-discontinuation of immunosuppression at 6 months and 4.5 years after transplantation. Demographic characteristics of the patients and the underlying liver diseases are shown in Table 1 according to whether they received FK 506 for either IAR or CR. All donor organs had been preserved in University of Wisconsin (UW) solution and were ABO compatible. The duration of patient follow-up was at least 4 months or until graft loss or death.

Immunosuppressive protocol

Methylprednisolone 10 mg/kg was given intravenously on induction of anaesthesia. Maintenance immunosuppression was based on a triple drug regime as follows (a) cyclosporin 2 mg/kg per day intravenously followed by oral cyclosporin to maintain whole blood trough levels in the range of 120–160 µg/l (TDx system monoclonal whole blood immunoassay); (b) azathioprine 1 mg/kg daily up to a maximum dose of 100 mg daily; (c) (methyl)prednisolone commencing at 40 mg per day with dose adjustment according to graft function. Acute rejection episodes were treated with either hydrocortisone 1 g twice daily intravenously for 3 days followed by 1 g daily intravenously for 2 days (1.6 g equivalent methylprednisolone dose over 5 days) or methylprednisolone 1 g intravenously for 3 days. Recurrent rejection episodes were treated with a further cycle of methylprednisolone 1 g intravenously for 3 days. Antilymphocyte globulin was not used and monoclonal anti-T cell antibody (OKT3) was given to one patient only.

Definition of intractable acute and chronic rejection

The diagnosis of rejection was based on accepted standard clinical and biochemical criteria and was confirmed by liver biopsy [2, 6, 14, 21]. A histopathological diagnosis of acute rejection required the presence of two or more of the following triad (a) an activated mononuclear cell infiltrate in portal tracts, (b) non-suppurative bile duct damage and (c) endothelitis or phlebitis of intrahepatic, hepatic or portal vein branches. Centrilobular necrosis was regarded as supportive but a non-obligatory feature of acute rejection. Intractable acute rejection was defined as ongoing graft dysfunction manifest by failure of liver biochemical tests to normalise [particularly serum bilirubin and aspartate transaminase (AST)] with histological evidence of ongoing rejection after at least two cycles of high dose supplemental steroids. Chronic rejection was divided into two categories: (a) vanishing bile duct syndrome (VBDS) when interlobular and septal bile ducts were absent from 50% or more of portal tracts or (b) early chronic rejection that showed, in serial liver biopsies, progressive loss of interlobular and septal bile ducts in the context of a progressive deterioration of liver biochemistry. Foam cell arteriopathy was considered a non-obligatory but supportive feature. All histological specimens were reviewed by a single pathologist (B.P.).

FK 506 'salvage' protocol

FK 506 was initiated at a dosage schedule of 0.1 mg/kg twice daily orally with dose adjustment based upon individual efficacy and toxicity profiles. If the serum bilirubin level exceeded 100 µmol/l, the

Table 1 Characteristics of patients ($n=28$) receiving FK 506 for graft salvage

	Indication for FK 506	
	Intractable rejection	Chronic rejection
No. grafts (n)	13	17
Patient age (median) (range)	39.5 years (24–56)	36 years (15–66)
Sex	5 male : 7 female	4 male : 13 female
Indication for transplantation		
Autoimmune CAH/cirrhosis		4
Fulminant hepatic failure		
a) Paracetamol overdose	–	1
b) NANB hepatitis	3	3
Hepatitis C related cirrhosis	1	3
Primary biliary cirrhosis	4	3
Primary sclerosing cholangitis	–	1
Tumour (APUDoma)	1	–
Secondary biliary cirrhosis	–	1
Retransplantation		
a) Hepatic artery thrombosis [a]	1	–
b) Chronic rejections [b]	2	1
c) Intractable rejection [c]	1	–

Underlying liver disease: [a] hepatitis C related cirrhosis; [b] Budd-Chiari syndrome, cryptogenic cirrhosis and primary sclerosing cholangitis; [c] primary biliary cirrhosis

dosage was reduced by 30–50% at 24 h after starting FK506 [1]. Cyclosporin was discontinued 24 h before starting FK506 to avoid potential nephrotoxicity and azathioprine was discontinued in all cases. The prednisolone dosage was changed to prednisolone 20 mg daily. An additional cycle of supplemental steroids, usually methylprednisolone, was given in some cases of intractable acute rejection if liver histology revealed a significant portal mononuclear cell infiltrate and/or endothelitis. FK506 plasma (separated at room temperature) levels were measured by enzyme-linked immunosorbent assay [18] but were not routinely available for clinical use nor was the FK506 dose adjusted to maintain specified blood levels. Incremental 25% dose reductions were made on the basis of possible toxicity, particularly a serum creatinine rise to more than 140 μmol/l and symptoms and/or signs indicative of neurotoxicity.

Statistical analysis

The χ^2 test was used to compare observed frequencies, the Wilcoxon test for paired data and the Mann-Whitney U test for unpaired data.

Results

In the intractable acute rejection group, rejection was reversed in 11 (84.6%) of 13 grafts after switching to FK506. Eleven (91.7%) of the 12 patients are currently alive, with a median survival of 439 (range 218–2045) days. The median duration of follow-up after conversion to FK506 was 279 (range 14–556) days for all patients and 279 (range 142–556) days for the 11 survivors. The one patient who lost two consecutive grafts died as a result of disseminated herpes simplex and fungal sepsis. Histology of both grafts revealed severe ongoing acute rejection following conversion to FK506 and, in the second instance, despite the subsequent use of two courses of OKT3. Performed lymphocytotoxic antibodies were not detected prior to transplantation for either graft.

Of the 17 cases of chronic rejection, 9 were classified as VBDS and 8 as early chronic rejection. With FK506, salvage of the graft was achieved in 10 (58.8%) of the 17 patients; these comprised 6 (75%) of the 8 patients with early chronic rejection and 4 (44%) of the 9 patients with VBDS (Fischer's exact test, $P = 0.37$). The median duration of follow-up after conversion to FK506 was 159 (range 9–824) days and 326 (range 122–824) days for the subgroup in which graft loss was prevented. Fourteen (82.4%) of the 17 patients are currently alive with a median survival of 737 (range 162–2925) days after initial transplantation. Of the seven patients in whom graft function continued to deteriorate despite switching to FK506, six were retransplanted. Three died in the early postoperative period and three are alive with good graft function. The need for retransplantation because of deteriorating graft function or death occurred at a median of 55.5 (range 9–106) days after conversion to FK506, and in the six who underwent retransplantation, histological examination of the failed allografts confirmed advanced VBDS in each instance.

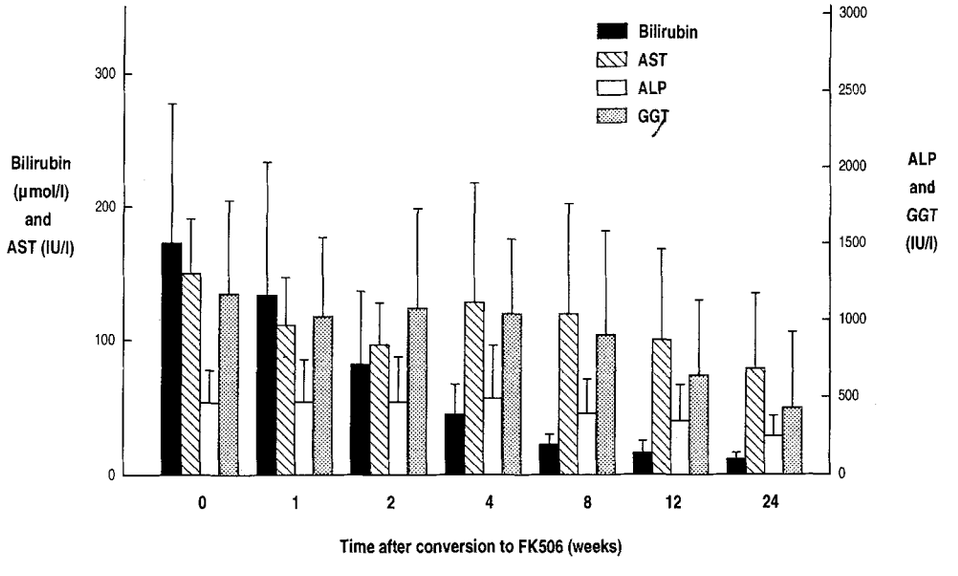

Fig. 1. Serial liver biochemistry after conversion to FK506 for intractable acute rejection. Values expressed as mean and 95% confidence intervals

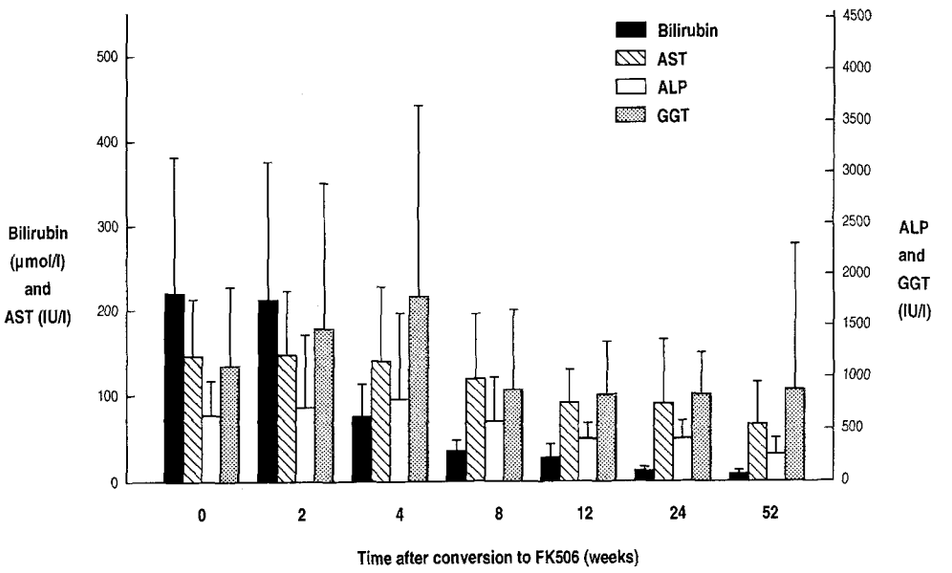

Fig. 2 Serial liver biochemistry after conversion to FK 506 for chronic rejection. Values expressed as mean and 95% confidence intervals

Effect of conversion to FK 506 on liver biochemistry

In the 11 patients with intractable acute rejection responding to FK 506, an improvement in serum bilirubin level was apparent by the end of the 1st week ($P < 0.005$) with a return to the normal range in 10 (91%) at a median of 2 (range 0.5–5) months (Fig. 1). The serum AST also fell significantly after the 1st week ($P < 0.025$) and returned to the normal range in 5 (45.5%) of the 11 responders, whilst both the serum alkaline phosphatase (ALP) and γ-glutaryl transferase (GGT) remained persistently abnormal in 9 of 11 cases.

A similar pattern in the liver biochemical profile was seen in the patients with chronic rejection (Fig. 2). In the ten responders, the serum bilirubin fell significantly in seven, and in all ten 1 month ($P = 0.012$); levels returned to the normal range at a median of 4 (range 0.5–7) months in nine of the ten responders. The serum bilirubin levels in those switched to FK 506 with early chronic rejection and VBDS were not statistically different ($P = 0.31$). In an analysis of the possible biochemical indicators of response, a serum bilirubin level of less than 200 μmol/l at the time of FK 506 conversion was found to be the best indicator of successful graft outcome (Fig. 3; specificity 100%, sensitivity 60%). Respective specificities and sensitivities using cut-off serum bilirubin levels of less than 250 and 300 μmol/l were 87.5 and 70.0%; and 72.7 and 80.0%. The serum AST also decreased slowly in the patients with chronic rejection, who responded with a decrease achieving statistical significance at 3 months after FK 506 conversion ($P < 0.05$) and returning to the normal range in five of the ten responders at a median of 4 (range 1–10) months. The elevation in serum ALP and GGT persisted and returned to the normal range in only one patient.

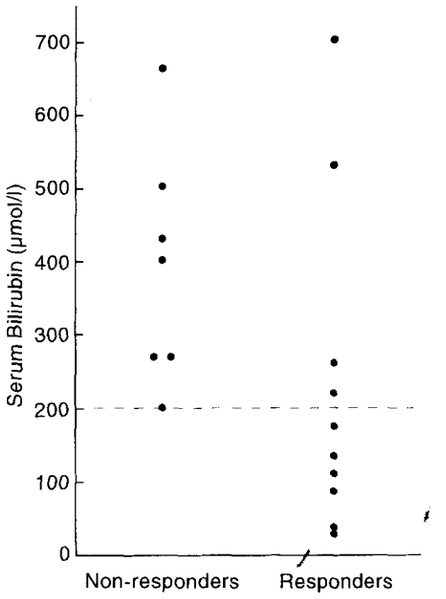

Fig. 3 Serum bilirubin prior to FK 506 in patients with chronic rejection

Graft dysfunction related to cytomegalovirus infection

Cytomegalovirus (CMV) infection occurred in 12 (42.9%) of the 28 patients (5 in the intractable rejection group, 7 in the chronic rejection group) as judged by seroconversion to IgM positivity, a 4-fold or greater rise in antibody titre or a combination of the two. CMV-associated disease developed in four patients with intractable rejection (hepatitis 3, pneumonitis 1) and in six of those with chronic rejectionn (hepatitis 3, hepatitis and pneumonitis 1, a systemic illness with fever and probable hepatitis 1). In two instances, CMV hepatitis preceded the development of chronic rejection, whilst the CMV disease manifested either simultaneously or following the diagnosis of intractable acute or chronic rejection in the remaining ten patients. All instances of CMV disease responded to a course of treatment with ganciclovir but recurrence of disease occurred in four patients after the drug was stopped. In two patients, one further course of treatment was required and another is on maintenance ganciclovir therapy after experiencing recurrent CMV hepatitis and pneumonitis. The fourth patient had four courses of ganciclovir, each associated with marked resolution of jaundice, before developing chronic rejection for which she was successfully switched to FK506 (Fig. 4).

Long-term FK506 dosage requirements

The FK506 requirement gradually decreased over time in responders, with achievement of a stable regimen between 2 and 3 months following conversion (Table 2). In the 11 patients in the intractable acute rejection group in whom long-term follow-up was available, the median FK506 dosage was 0.13, 0.17, 0.16, 0.13, 0.12 and 0.11 mg/kg per day at 0, 0.5, 1, 2, 3 and 6 months, respectively, after conversion. Comparable dosage requirements for the ten patients with chronic rejection successfully converted to FK506 were 0.14, 0.15, 0.17, 0.15, 0.13 and 0.10 mg/kg per day, with the same requirement at 1 year. Corresponding FK506 plasma levels diminished with time, with median levels at 1 and 2 weeks and 1, 2, 3 and 6 months of 0.50, 0.35, 0.41, 0.31, 0.27 and 0.25 ng/ml in the intractable acute rejection group and 0.52, 0.50, 0.81, 0.40, 0.47 and 0.48 in the chronic rejection group, and 0.25 ng/ml at 1 year in this group.

Corticosteroids were successfully discontinued in 7 (63.6%) of 11 patients with intractable rejection at a median of 5 months (range 2–14) after conversion to FK506. The remaining 4 (36.4%) patients remained on a low dose of prednisolone [median 7.5 mg (range 5–10)] 3 to 4 months following conversion. In four (40%) of the ten patients successfully treated for chronic rejection, corticosteroids were withdrawn at a median of 5.5 months

Table 2 FK 506 dosage requirements and plasma levels in the patients during successful graft salvage (*NA* not applicable)

Time	Intractable rejection ($n = 1$)			Chronic rejection ($n = 10$)		
	FK 506 dose[a]		Plasma level[a] (ng/ml)	FK 506 dose		Plasma level (ng/ml)
	(mg/day)	(mg/kg per day)		(mg/day)	(mg/kg)	
Initiation	10 (4–10)	0.13 (0.05–0.20)	NA	8 (4–12)	0.14 (0.06–0.20)	NA
1 week	10 (6–16)	0.16 (0.08–0.24)	0.5 (0.27–0.68)	8 (4–12)	0.14 (0.06–0.20)	0.52 (0.18–1.15)
2 weeks	10 (6–16)	0.17 (0.10–0.23)	0.35 (0.15–1.24)	9 (4–12)	0.15 (0.06–0.20)	0.5 (0.15–1.28)
1 month	10 (6–16)	0.16 (0.08–0.27)	0.41 (0.08–1.98)	10 (4–12)	0.17 (0.06–0.20)	0.81 (0.21–1.49)
2 months	8 (4–16)	0.13 (0.05–0.27)	0.31 (0.08–1.27)	8 (4–12)	0.15 (0.05–0.20)	0.4 (0.34–0.89)
3 months	8 (4–16)	0.12 (0.05–0.27)	0.27 (0.10–0.67)	8 (4–12)	0.13 (0.05–0.20)	0.47 (0.27–0.58)
6 months	8 (3–14)	0.11 (0.05–0.23)	0.25 (0.12–0.45)	6 (4–14)	0.1 (0.06–0.26)	0.48 (0.14–0.67)
9 months	NA	NA	NA	6.5 (4–10)	0.1 (0.07–0.16)	0.45 (0.15–0.75)
12 months	NA	NA	NA	6.5 (4–10)	0.1 (0.07–0.16)	0.25 (0.15–0.44)

[a] Median (range)

Table 3 Frequency of side-effects associated with FK 506 ($n = 28$)

Side-effect	Intractable rejection (n)	Chronic rejection (n)	Total (%)
Renal impairment	6	3	9 (32.1)
Diabetes	5	3	8 (28.6)
Hypertension	2	3	5 (17.9)
Headache	3	3	6 (21.4)
Tremor	1	1	2 (7.1)
Neuropathy	0	1	1 (3.6)
Hair loss	1	1	2 (7.1)

(range 0.5–17). The remaining six (60%) remained on a median dose of 5 mg (2.5–15) of prednisolone at 1–15 months.

Adverse effects

In an analysis of possible FK 506-related toxicity, adverse events included renal impairment (32.1%), onset of newly diagnosed diabetes mellitus (28.6%), headache (21.4%) and hypertension requiring antihypertensive drugs (17.9%; Table 3). Renal impairment was always reversible and responded promptly to a reduction in the FK 506 dosage. No patient required dialysis. Diabetes mellitus was often first apparent during concurrent administration of high dose corticosteroids. Two patients required oral hypoglycaemic agents and three patients are on long-term insulin therapy to maintain glucose haemostasis. One patient was able to be converted from insulin to oral hypoglycaemic agents, whilst a further two patients also initially requiring insulin were able to be weaned off insulin completely. The improved blood glucose control occurred with gradual reduction in, and in some cases discontinuation of, corticosteroids and reduction in FK 506 dosage. Neurological symptoms and signs including headache and tremor also generally responded to dosage reduction. One patient treated for chronic rejection and who was markedly jaundiced developed a peripheral neuropathy that gradually reversed with time after reduction in FK 506 dosage. The hypertension was easy to control with a calcium antagonist or a beta-blocking agent.

Discussion

The response rate of intractable and chronic allograft rejection to FK 506 rescue therapy observed in the present series was remarkable and represented a substantial reduction in the need for retransplantation. In the intractable acute rejection group, successful graft salvage was achieved in 84.6% of cases with a normalisation of serum bilirubin in all, while in chronic rejection, 58.8% of the grafts were salvaged. In responders, a fall in serum bilirubin was invariably present by the end of the 1st week in those with intractable acute rejection switched to FK 506, and was seen within 2 weeks in the majority of patients (70%) with chronic rejection, whereas it increased in all the non-responders. In the chronic rejection group, we found that a serum bilirubin level immediately prior to conversion to FK 506 of less than 200 μmol/l had a 100% specificity and 60% sensitivity of predicting a successful response. We could not confirm that the serum transaminase level or any other liver enzyme was a useful indicator of response as described in the US multicentre FK 506 Liver Study Group report [19]. Our data, therefore, suggested that it is possible to determine which patients will respond in the long-term to FK 506 an earlier stage than the 1 month noted in previous studies [9, 10].

As in previous reports, patients with early chronic rejection had a better response rate than those with VBDS (75% *versus* 44%). While data from the US multicenter FK 506 Liver Study Group [19] have indicated that pathological findings are not an independent prognostic factor when the impairment in liver function, as assessed by total bilirubin and serum transaminase levels, is controlled for, the serum bilirubin levels before FK 506 treatment in our patients with chronic rejection were similar in the two groups.

This series differed from those previous studies in which intractable acute rejection is usually defined as a failure of medical management after at least one course of OKT3 in addition to one or two cycles of high dose steroids. Although all our cases had been treated with at least two cycles of high dose steroids, it could be argued that our patients had less severe 'intractable' acute rejection and, therefore, were more likely to respond to FK 506. OKT3 was rarely used because of its associated short-term morbidity and substantial long-term risk of lymphoproliferative disorders. Furthermore, OKT3 was used unsuccessfully in one case after the development of intractable rejection in her second graft despite conversion to FK 506. In the cases of chronic rejection, OKT3 is never of benefit and was, therefore, not used. Thus, FK 506 was particularly effective in the treatment of intractable acute cellular rejection and seemed to have a better side-effect profile and a similar response rate to OKT3 when compared to previously published reports. However, a controlled study would be needed to resolve this [3, 15, 16, 23].

Adverse effects related to FK 506 in the present study were, in general, mild and frequently resolved with dosage reduction. The lack of serious toxicity may be explained by the fact that intravenous FK 506 was not given, as in previous studies, and that the initial FK 506 dose was carefully individualised taking into account the baseline liver graft function, which may affect blood levels [1]. Of considerable overall benefit to the patient was that the discontinuation of corticosteroids in a significant proportion of patients facilitated better diabetic control and the reduction or withdrawal of insulin and improved control of coexisting hypertension.

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