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# Two-year data from the European multicentre tacrolimus (FK506) liver study

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**Abstract** To provide a more definitive assessment of the efficacy and safety of tacrolimus therapy in comparison with cyclosporin, the extended follow-up of the European multicentre study is reported. Two-year Kaplan-Meier estimates indicated significant reductions in acute (tacrolimus 45.4 %, cyclosporin 55.8 %; $P = 0.006$), refractory (1.2 % versus 6.4 %; $P = 0.003$) and chronic rejection (2.0 % versus 6.9 %; $P = 0.015$) despite significantly lower steroid usage in patients receiving tacrolimus therapy. Patient and graft survival rates (80.6 % versus 74.8 % and 74.5 % versus 70.0 %, respectively) were also superior, although these failed to reach statistical significance. Safety profiles were comparable for most major categories (including renal, neurological and glucose metabolic disorders) and in certain aspects were more favourable for tacrolimus. Hypertension (28.0 % versus 39.6 %, $P < 0.01$) and cytomegalovirus infection (14.8 % versus 22.3 %, $P < 0.01$), two events with important long-term clinical consequences, were reported significantly less frequently. Hirsutism (0.0 % versus 8.7 %, $P < 0.01$) and gum hyperplasia (0.0 % versus 2.3 %, $P < 0.05$) were absent in patients receiving tacrolimus. Tacrolimus appears to provide effective and safe long-term immunosuppression.

**Key words** Tacrolimus · Cyclosporin · Comparative study · Primary liver transplantation · Immunosuppressive treatment failure

## Introduction

Preliminary clinical studies conducted at the University of Pittsburgh demonstrated that tacrolimus (FK506) was both safe and effective when administered as primary therapy to liver transplant recipients. Comparison with an historical cohort of cyclosporin-treated controls indicated that tacrolimus therapy was associated with significantly better patient and graft survival rates and a significant reduction in the incidence of rejection [16]. A prospective, controlled study was subsequently undertaken by the same group; patient and graft survival rates at 12 months were reported to be 93 % and 90 %, respectively, for patients receiving tacrolimus

therapy compared with 81% and 70% for the cyclosporin control group [8].

Based on these encouraging results, two international, open-label, multicentre, randomised comparative studies were conducted (one in Europe and the second in the United States). Their objective was to compare the efficacy and safety of tacrolimus- and cyclosporin-based therapy in patients undergoing primary liver transplantation. Details of the results at both 6 months [2, 4, 5, 9, 11, 12, 17] and 1 year [1, 3, 6, 7, 10, 14, 15] have been published previously. This report presents the continued follow-up of the 529 patients evaluated in the European multicentre trial.

## Methods

### Patient eligibility

This study was conducted at eight centres in four European countries (France, Germany, Sweden and the United Kingdom). Male and female patients, 18–70 years of age, with end-stage liver disease requiring transplantation were eligible for entry. Patients were excluded if they had serological evidence of HIV, diagnoses of active neoplastic disease or primary liver cancer with evidence of metastases, arteritis or vasculitis, if they were undergoing multiple organ transplantation or had previously received a liver allograft. Women who were pregnant or who were using inadequate contraceptive measures were also excluded. Formal approval for the conduct of the study was obtained from the ethics committees of the participating centres prior to enrolment and informed consent was received from each patient. This study was performed in accordance with the Declaration of Helsinki.

Prior to transplantation, patients were equally and randomly assigned to treatment within centres. Patients were stratified for the presence of fulminant hepatic failure. Treatment consisted of either tacrolimus and low-dose steroids or the optimal, centre-specific cyclosporin-based regimen (cyclosporin, azathioprine, steroids ± ALG). Full details of the immunosuppressive regimens administered have been published previously [1, 6].

### Evaluation of efficacy and safety: statistical analysis

The primary efficacy variables were the incidences of acute, refractory acute and chronic rejection, steroid usage, and patient and graft survival. Safety was assessed in terms of spontaneously reported adverse events and/or significant changes in laboratory parameters, irrespective of any causality in relation to the study medication.

The sample size (414 evaluable patients, 207 per treatment group) was calculated to detect a 10% difference in survival rates at 12 months between tacrolimus- and cyclosporin-treated patients with a power of at least 80% (log-rank test), assuming an 80% 1-year survival rate for patients receiving conventional therapy. The time to the first biopsy-proven rejection, and patient and graft survival were summarised by Kaplan-Meier methodology; differences between the survival curves were analysed with the generalised Wilcoxon test. The incidences of rejection were compared with the Cochran-Mantel-Haenszel procedure, the Mann-Whitney U-test was used to compare cumulative steroid doses and Fisher's exact test was applied to test for any differences in adverse event incidence rates.

## Results

Five hundred and forty-five patients (294 men, 251 women, aged 15–68 years) were enrolled into this study between September 1990 and February 1992. Sixteen of these patients (tacrolimus 5, cyclosporin 11) did not receive study medication and were excluded from the efficacy analysis. A further 5 patients were misrandomised (tacrolimus 3, cyclosporin 2); data from these patients were evaluated and were attributed to the treatment that they received. The population for analysis, therefore, constituted 529 patients, 264 of whom received treatment with tacrolimus and 265 with cyclosporin.

The mean age of the patients was similar for both treatment groups although the proportion of male and female patients differed ($P = 0.021$). The two treatment groups were well matched in terms of baseline characteristics (primary diagnoses, stage of hepatic encephalopathy, urgency of transplant, mean donor age, assessment of liver prior to reperfusion, total ischaemia time and preservation fluid utilised).

The median oral tacrolimus dose administered was progressively reduced throughout the course of the study (month 1: 0.152 mg/kg; months 2–3: 0.142 mg/kg; months 4–6: 0.116 mg/kg; months 7–12: 0.089 mg/kg; months 13–18: 0.073 mg/kg; months 19–24: 0.069 mg/kg). A similar decline in median oral cyclosporin doses was also noted changing from 8.01 mg/kg during month 1 to 3.47 mg/kg for the 19–24-month period.

Two hundred and nine patients (39.5%) were withdrawn from the study during the 24-month treatment period [tacrolimus 98 (37.1%), cyclosporin 111 (41.9%)], 19 of whom were withdrawn between months 13 and 24 [tacrolimus 11 (4.2%), cyclosporin 8 (3.0%)]. The proportion of patients withdrawn as a result of experiencing adverse events was marginally higher in the tacrolimus treatment group than in patients receiving cyclosporin therapy [tacrolimus 82 (31.1%), cyclosporin 67 (25.3%)]. In contrast, the number of patients withdrawn as a result of 'intractable' rejection was significantly lower in the tacrolimus treatment group [tacrolimus 7 (2.7%), cyclosporin 27 (10.2%); $P < 0.001$)].

### Efficacy analysis

#### *Rejection*

Kaplan-Meier estimates of the primary efficacy endpoints at 24 months indicated that there were significant reductions in the incidences of acute (Fig. 1, $P = 0.006$), refractory acute ($P = 0.003$) and chronic rejection ($P = 0.015$) for patients receiving tacrolimus therapy.

A total of 285 acute rejection episodes were reported (tacrolimus 133, cyclosporin 152), 204 of which were ex-

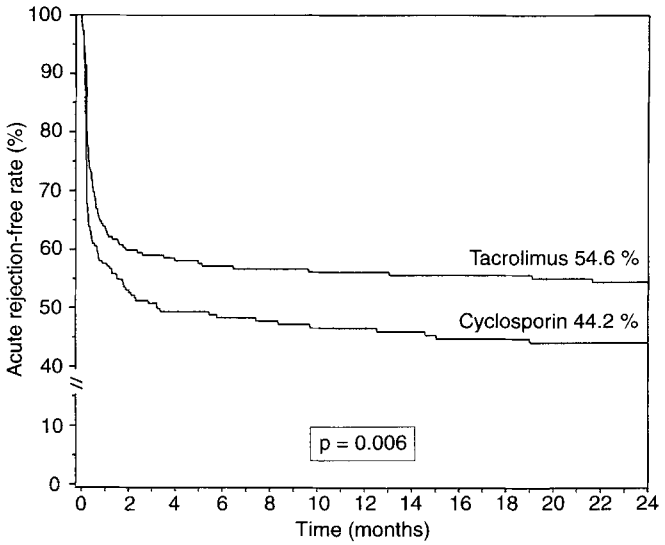


**Fig. 1** Kaplan-Meier estimates of patients with acute rejection

**Table 1** Immunosuppressive treatment failures

| | Number of patients (%) | | *P* value |
|---|---|---|---|
| | Tacrolimus | Cyclosporin | |
| Refractory acute rejection | 3 (1.1) | 16 (6.0) | 0.005 |
| Chronic rejection | 4 (1.5) | 14 (5.3) | 0.032 |

**Table 2** Steroid usage

| Prednisone dose (mg per day) | Percentage of patients | |
|---|---|---|
| | Tacrolimus ($n = 166$) | Cyclosporin ($n = 153$) |
| 0 | 48.2 | 22.9 |
| > 0–≤ 2.5 | 6.6 | 14.4 |
| > 2.5–≤ 5.0 | 24.1 | 30.7 |
| > 5.0–≤ 7.5 | 4.8 | 8.5 |
| > 7.5–≤ 10.0 | 11.4 | 14.4 |
| > 10.0–≤ 12.5 | 2.4 | 3.3 |
| > 12.5–≤ 15.0 | 1.8 | 3.3 |
| > 15.0–≤ 20.0 | 0.0 | 2.6 |
| > 20.0 | 0.6 | 0.0 |
| Mean dose | 3.35 ± 4.31 | 5.16 ± 4.42 |

perienced during the first four weeks of treatment (tacrolimus 95, cyclosporin 109). A further 58 episodes (tacrolimus 27, cyclosporin 31) were reported before the end of month 6, 11 (tacrolimus 6, cyclosporin 5) between months 7 and 12, and 12 (tacrolimus 5, cyclosporin 7) between months 13 and 24. Of the 133 episodes of acute rejection experienced by patients receiving tacrolimus therapy, 105 (78.9 %) resolved following treatment with supplemental steroids alone compared with 108 of the 152 episodes (71.1 %) in cyclosporin-treated patients. The severity of these acute rejection episodes, as assessed histologically, was also reduced in patients receiving tacrolimus therapy with fewer patients experiencing grades of moderate, moderate/severe and severe rejection.

*Immunosuppressive treatment failures (Table 1)*

Thirty cyclosporin-treated patients were classified as immunosuppressive treatment failures (i.e. with diagnoses of either refractory acute or chronic rejection), of whom 14 were converted to tacrolimus therapy, 2 continued to receive treatment with cyclosporin, 11 were retransplanted and 3 died. Of the 14 switched to tacrolimus therapy, 8 were alive with their original graft (including 4 who were converted with histologically-proven chronic rejection), 1 was retransplanted and 5 had died by the end of the 24-month follow-up period. Seven tacrolimus-treated patients were considered to be immunosuppressive treatment failures, 3 of whom were converted to cyclosporin therapy in an attempt to salvage their graft (1 patient died and 2 required retransplanting). Of the remaining 4, 1 patient died, 2 underwent retransplantation (both of whom were alive at the end of the follow-up period), and 1 continued to receive treatment with tacrolimus (again, this patient was alive at month 24).

*Steroid usage*

The cumulative steroid dose during the 24-month treatment period, administered either as prophylaxis or for the treatment of rejection, was significantly reduced in the tacrolimus treatment group. The median intravenous dose was 21.5 mg/kg for tacrolimus-treated patients and 28.0 mg/kg for patients receiving cyclosporin therapy ($P = 0.028$). Corresponding figures for oral usage were 71.0 mg/kg and 87.6 mg/kg, respectively ($P = 0.008$). Details of the maintenance steroid dose administered at month 24 and the number of patients remaining in the study in whom steroid therapy was successfully withdrawn are presented in Table 2.

*Patient and graft survival*

Patient death was self-explanatory whereas graft failure reflected the combined losses resulting from retransplantation and/or death. Kaplan-Meier estimates of 24-month patient and graft survival were approximately 5 % higher in patients receiving tacrolimus therapy but this difference failed to reach statistical significance (Fig. 2). One hundred and nineteen deaths were recorded during the 24-month follow-up period, but only

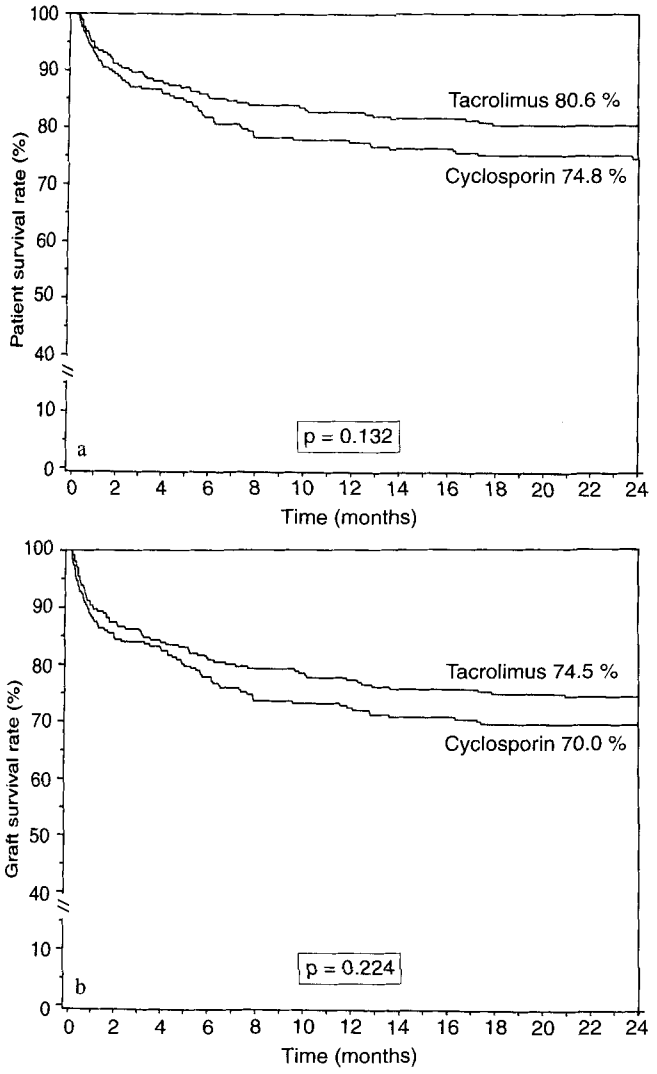


**Fig. 2a,b** Kaplan-Meier estimates of **a** patient survival and **b** graft survival for the tacrolimus and cyclosporin treatment groups

13 of these were encountered between months 13 and 24. In total, 57 patients were retransplanted, 25 (9.5 %) from the tacrolimus treatment group compared with 32 (12.1 %) receiving cyclosporin therapy. Nine of the 25 tacrolimus-treated patients (36.0 %) subsequently died compared with 19 of the 32 patients (59.4 %) receiving cyclosporin. Causes of patient and graft loss during the second year of the study are listed in Table 3.

## Safety analysis

Over the 24-month treatment period, 82 tacrolimus-treated patients (31.1 %) experienced adverse events that led to withdrawal compared with 67 patients (25.3 %) receiving cyclosporin therapy. The majority of these events occurred within the initial 6-month treatment period (with approximately 50 % of these occurring within the first month). Subsequently, 19 patients (tacrolimus 10, cyclosporin 9) were withdrawn between months 7 and 12, and a further 14 (tacrolimus 6, cyclosporin 8) between months 13 and 24.

**Table 3** Causes of patient and graft loss

| | Number of patients (%) | |
|---|---|---|
| | Tacrolimus ($n$ = 179) | Cyclosporin ($n$ = 166) |
| **Causes of death** | | |
| Bronchopneumonia | 0 (0.0) | 1 (0.6) |
| Cardiovascular failure | 1 (0.6) | 0 (0.0) |
| Hepatic infarction | 0 (0.0) | 1 (0.6) |
| Hepatitis B recurrence | 1 (0.6) | 0 (0.0) |
| Hypoxic brain damage | 0 (0.0) | 1 (0.6) |
| Metastases – cholangiocarcinoma | 0 (0.0) | 1 (0.6) |
| Prolonged septicaemic breakdown | 0 (0.0) | 1 (0.6) |
| Recurrent hepatocellular carcinoma | 1 (0.6) | 3 (1.8) |
| Septic shock | 1 (0.6) | 0 (0.0) |
| Urosepsis | 1 (0.6) | 0 (0.0) |
| **Causes of graft failure** | | |
| Death | 4 (2.2) | 6 (3.6) |
| Retransplantation | | |
| Chronic rejection | 0 (0.0) | 2 (1.2) |
| Fulminant hepatitis | 1 (0.6) | 0 (0.0) |
| Ischaemic-type biliary lesion | 1 (0.6) | 0 (0.0) |
| Recurrence of Budd-chiari disease | 1 (0.6) | 0 (0.0) |

Adverse event occurrence rates listed below (Tables 4–6) are for those events assessed as being causally related to treatment. Events, for example, reported during month 2 that only subsequently resolved at month 14 would have been counted for the purposes of the analysis during months 2–6, 7–12 and 13–18, respectively.

In terms of the adverse events reported during the second year of this study, there was little difference between the two treatment groups in their incidence, type or nature. No significant differences were observed in the occurrence of abnormal renal function (a term incorporating the COSTART codes abnormal kidney function, and increased creatinine and blood urea concentrations), glucose metabolism disorders (hyperglycaemia and diabetes mellitus combined) and neurological complications (except tremor which was more prevalent in the tacrolimus treatment group between months 13 and 18) (Table 4). Hypertension, however, was experienced by significantly fewer patients receiving tacrolimus therapy both between months 13 and 18, and 19–24.

The incidences of infection and benign and malignant neoplasm were analysed over the 24-month treatment period (Tables 5, 6, respectively). Two of the main clinical categories of infection, namely cholangitis and

**Table 4** Frequency of adverse events

| Adverse event | Percentage of patients Months 13–18 | | *P* value | Percentage of patients Months 19–24 | | *P* value |
|---|---|---|---|---|---|---|
| | Tacrolimus ($n = 179$) | Cyclosporin ($n = 166$) | | Tacrolimus ($n = 168$) | Cyclosporin ($n = 153$) | |
| **Renal impairment** | | | | | | |
| Abnormal renal function | 23.5 | 21.7 | | 20.8 | 21.6 | |
| Hypertension | 19.0 | 31.9 | 0.006 | 18.5 | 28.8 | 0.035 |
| **Changes in glucose metabolism** | | | | | | |
| Hyperglycaemia/diabetes mellitus | 16.8 | 11.4 | | 16.1 | 9.4 | |
| **Neurological complications** | | | | | | |
| Headache | 16.2 | 18.7 | | 20.2 | 20.9 | |
| Insomnia | 5.6 | 6.6 | | 5.4 | 1.3 | |
| Paraesthesia | 6.1 | 4.2 | | 4.2 | 4.6 | |
| Tremor | 33.5 | 18.7 | 0.002 | 21.4 | 16.3 | |

**Table 5** Frequency of infectious complications

| Adverse event | Percentage of patients Months 1–24 | | *P* value |
|---|---|---|---|
| | Tacrolimus ($n = 264$) | Cyclosporin ($n = 265$) | |
| Cholangitis | 14.8 | 15.8 | |
| Cytomegalovirus infection | 14.8 | 22.3 | 0.033 |
| Pneumonia | 13.6 | 20.4 | |
| Urinary tract infection | 16.3 | 15.8 | |

**Table 6** Frequency of benign and malignant neoplasm

| Adverse event | Percentage of patients Months 1–24 | |
|---|---|---|
| | Tacrolimus ($n = 264$) | Cyclosporin ($n = 265$) |
| Breast neoplasm | 0.4 | 0.0 |
| Lymphoma-like reaction | 0.8 | 0.4 |
| Other neoplasms | 2.3 | 3.4 |
| Skin benign neoplasm | 0.0 | 1.1 |

urinary tract infection, did not differ in incidence between the two treatment groups. Pneumonia was reported less frequently and the incidence of cytomegalovirus (CMV) infection was significantly reduced in patients receiving tacrolimus therapy (tacrolimus 14.8 %, cyclosporin 22.3 %; $P = 0.033$). Neoplasms had been diagnosed in 22 patients by month 24 (Table 6), 9 of whom received tacrolimus and 13 cyclosporin therapy.

Hirsutism (tacrolimus 0.0 %, cyclosporin 8.7 %; $P < 0.01$) and gum hyperplasia (tacrolimus 0.0 %, cyclosporin 2.3 %; $P < 0.05$) were both reported by significantly fewer patients receiving tacrolimus therapy.

## Discussion

In contrast to the US multicentre study, severely decompensated cirrhotic patients with renal impairment, patients with primary carcinoma of the liver and severely ill patients with fulminant hepatic failure were included in this trial. This accounts for the somewhat lower overall patient and graft survival figures (1-year patient and graft survival rates for the US study were 88 % and 82 %, respectively, for the tacrolimus treatment group 88 % and 79 % for patients receiving cyclosporin therapy [15]). With the exception of children, the exclusion criteria used in the trial reported here were limited to those patients in whom it would normally be considered inadvisable to perform primary liver transplantation. The study population was, therefore, representative of patients requiring transplantation in everyday clinical practice.

The primary determinant of treatment efficacy was the prevention of rejection. Tacrolimus therapy was associated with a significant reduction in the frequency of rejection (acute, refractory and chronic) despite significantly lower steroid usage. The decreased incidence in immunosuppressive treatment failure for patients receiving tacrolimus therapy is of considerable clinical benefit and was reflected by a reduced requirement for retransplantation.

The improvement in overall patient and graft survival for the tacrolimus treatment group failed to reach statistical significance, but this was, at least in part, related to the use of an intent-to-treat analysis [13]. Those patients converted from cyclosporin to tacrolimus therapy as a result of inadequate rejection control, and in whom grafts were subsequently 'salvaged', were nevertheless assigned to the cyclosporin arm for the final comparison.

One might have expected a higher incidence of infection to be associated with the greater immunosuppressive potency of tacrolimus therapy. This was not apparent; the main clinical categories of infection did not dif-

fer and there was a significant reduction in the incidence of CMV infection in tacrolimus-treated patients. This latter observation is an important finding in terms of reducing patient morbidity.

It is unclear whether the reduced incidence of hypertension observed in this study was the result of lower steroid usage or whether this represents an intrinsic benefit associated with tacrolimus therapy. In either eventuality, it is a significant advantage for patients receiving treatment with tacrolimus therapy over conventional cyclosporin-based immunosuppression. This advantage will be of particular benefit for the paediatric population but could have important long-term clinical consequences for all patients receiving tacrolimus therapy.

Insulin usage and the development of new-onset diabetes mellitus have in many cases been attributed to steroid therapy; however, the diabetogenic effects of both tacrolimus and cyclosporin have been documented previously. The extended follow-up of the present study would tend to indicate that there is no significant difference in the degree of diabetogenicity between the two immunosuppressive regimens administered during the course of this study.

The clinical significance of the reported neurological and nephrological events have been discussed previously [3, 7]: the conclusions drawn being that the type, incidence and severity of these events were comparable between the tacrolimus and cyclosporin treatment groups. Minor neurological symptoms (including tremor, headache, insomnia, and paraesthesia) were not considered to have significant clinical relevance and did not appear to interfere with daily activities whereas major complications were considered to be reversible. Acute renal failure appeared to be reversible with no long-term damage being observed.

Again on the positive side for tacrolimus, the absence of hirsutism and gum hypertrophy is very much welcomed by the patient.

It should be borne in mind that none of the eight participating centres had previous clinical experience of administering tacrolimus therapy when this trial was initiated. During the early part of the study, tacrolimus therapeutic drug monitoring proved to be somewhat problematic as the available technique (ELISA) was both time consuming and unreliable. With little or no blood level information available, dose modifications were implemented following signs of rejection or suspicion of drug-related toxicity. Early experience indicated that the doses recommended initially were inappropriately high and this led to a marked reduction in the dose of tacrolimus being administered. Only later was a rapid and locally available assay introduced to assist with therapeutic drug monitoring. In contrast, cyclosporin blood concentrations were used to determine, and subsequently adjust, the dose both during the early post-operative period and throughout the course of the study. If tacrolimus blood level monitoring had been available from the outset of this study then some of the problems encountered in the early postoperative period may have been prevented. In addition, as further clinical experience is gained with tacrolimus, it has to be expected that the overall risk-benefit ratio will improve.

In conclusion, the demonstrated superiority of tacrolimus therapy over the 2-year follow-up period in terms of significant reductions in the incidence of acute, refractory acute and chronic rejection, is translated into a shorter and less problematic convalescent period. The reduced requirement for corticosteroids is also of direct benefit to the patient. The safety profile associated with tacrolimus therapy, although similar to that for cyclosporin in major categories, is in certain respects more favourable provided that careful attention is paid to the doses administered on the basis of clinical and blood level assessments.

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