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Efficacy and safety of oral low-dose tacrolimus treatment in liver transplantation

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Abstract Eighty-four adult patients were recruited from four centres in Spain to evaluate the efficacy and safety of low-dose (0.1 mg/kg per day) oral tacrolimus plus corticosteroid immunosuppression in liver transplantation. The median daily dose of tacrolimus was increased during the first 3 weeks of therapy from an initial dose of 0.1 mg/kg per day to a maximum of 0.145 mg/kg per day and was subsequently decreased gradually to a minimum of 0.076 mg/kg per day at 1 year. At 7 days posttransplantation, 87.7% of patients had trough whole blood levels of tacrolimus within the therapeutic range (5–20 ng/ml), and the median levels remained fairly constant during the rest of the year (10.1–11.8 ng/ml). None of the patients required intravenous administration of tacrolimus. At 1 year, Kaplan-Meier estimates showed that 73.8% of the patients were receiving tacrolimus monotherapy without the need for corticosteroids. One-year patient and graft survival were 75.9% and 72.3%, respectively. The incidence of acute rejection was 51.2%; 9.5% of cases resolved spontaneously without antirejection therapy and 10.7% were corticosteroid resistant. Only 1 patient (1.2%) developed chronic rejection. The most important adverse events were hypertension (45.2%), tremor (44.0%), diabetes mellitus (33.3%), diarrhoea (31%) and nephrotoxicity (29.8%). Severe neurotoxicity-like convulsions (4.8%), dysarthria (9.5%), delirium (1.2%), coma (1.2%) and the need for haemodialysis (3 patients) were uncommon. In conclusion, low-dose oral tacrolimus immunosuppression is associated with low toxicity without compromising efficacy.

Key words Liver transplantation · Tacrolimus · Rejection · Toxicity

Introduction

Tacrolimus was first used as an immunosuppressive agent in clinical liver transplantation at the University of Pittsburgh in 1989 [2, 4, 6]. More recently, two large, multicentre, randomised studies comparing tacrolimus with cyclosporin-based protocols have been undertaken in the USA [5] and Europe [1, 8]. These studies demonstrated a significant reduction in acute, refractory acute and chronic rejection with tacrolimus therapy compared with cyclosporin. However, there was no significant difference in the estimated rates of patient and graft survival at 1 year. In addition, while the spectrum of adverse events was similar in both groups, their incidence was higher in the tacrolimus arm, particularly during the early part of the study, before an amendment to the study protocol led to a reduction in the dose of tacrolimus. Nevertheless, hypertension was significantly lower in the tacrolimus group and gum hyperplasia and hirsutism did not occur in any patient. Tacrolimus was given intravenously during the first few days posttransplantation, with conversion to oral administration as early as

possible. The decreased dose of tacrolimus was found to result in a lower incidence of adverse events without compromising efficacy. Based on this experience, a new protocol for administration of tacrolimus was proposed, involving a decreased dose compared with that used in previous studies and immediate administration via the oral route, provided that tacrolimus absorption was bile independent. The objective of this study was to evaluate the efficacy and safety of low-dose, oral tacrolimus in combination with corticosteroids over a period of 12 months after liver transplantation.

Materials and methods

This multicentre, open-label, non-randomised, non-comparative study was undertaken between July 1993 and May 1995 in four centres in Spain. The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the local ethics committees and each patient gave written informed consent before participation.

Patient eligibility

Male and female adult patients of all ages with end-stage liver disease requiring transplantation were eligible for entry into the study. Exclusion criteria were limited to evidence of extrahepatic neoplastic disease, serological evidence of human immunodeficiency virus, the need for transplantation of organs other than the liver and irreversible renal failure. Patients receiving an ABO-incompatible graft and women who were pregnant or using inadequate contraceptive measures were also excluded. However, patients with fulminant hepatic failure and those receiving a second liver transplant were included in the study.

Immunosuppressive protocol

Tacrolimus was administered at an initial dose of 0.05 mg/kg twice daily (0.1 mg/kg per day). The first dose was given within 6 h of liver transplantation via a nasogastric or nasoduodenal tube. Subsequent doses were administered at 12-h intervals with conversion to oral administration as soon as the patient was able to tolerate oral feeding. Whole blood trough levels of tacrolimus were monitored daily for the first 14 days post-transplantation and subsequently at each outpatient visit. The concentration of tacrolimus was measured using a semi-automated microparticle enzyme immunoassay method based on the Abbott IMx analyser. For the purposes of this study, the accepted therapeutic window for whole blood trough levels of tacrolimus was 5–20 ng/ml. Dosage adjustments were made throughout the study of maintain blood levels within this therapeutic range, or to control toxicity or graft rejection when necessary.

Corticosteroid treatment was initiated on the day of transplantation. Patients received 1 g of methylprednisolone before graft reperfusion, followed by 200 mg tapered over 5 days to 40 mg. By day 7 posttransplantation, the dose of oral methylprednisolone was reduced to 20 mg and continued until month 3, after which the dose was further gradually reduced. After month 6, patients were considered for discontinuation of corticosteroid treatment.

Management of rejection

Diagnosis of rejection was based on clinical symptoms and laboratory data, with confirmation by liver biopsy. Treatment of acute rejection consisted of an increase in the dose of tacrolimus if whole blood trough levels were low, and/or a 0.5–1 g bolus dose of methylprednisolone for 3 days. In patients with corticosteroid-resistant rejection, 5 mg/day OKT3 (Orthoclone; Cilag) or antithymocyte globulin (ATG) was given for 7–14 days. If signs of rejection did not resolve, the patient was diagnosed as having refractory rejection and was withdrawn from the study.

Evaluation of efficacy and safety

The primary efficacy parameters of the study were patient and graft survival, which were estimated using Kaplan-Meier analysis. Secondary efficacy endpoints were the incidence of acute and chronic rejection. Acute rejection episodes were classified according to the response to antirejection treatment as spontaneously resolving, corticosteroid-sensitive, corticosteroid-resistant or refractory rejection. Chronic rejection was defined histologically. Corticosteroid use, discontinuation of corticosteroids and the need for the introduction of other immunosuppressive agents, such as azathioprine, OKT3 or ATG, were also evaluated. Evaluation of safety included all serious adverse events and drug toxicity leading to a reduction in the dose or interruption of tacrolimus therapy, including renal dysfunction, diabetes mellitus, hypertension, neurotoxicity and infectious complications.

Results

Patient population

Eight-four adult patients (60 males, 24 females), with a median age of 50 years (range 19–64) were recruited into the study from the four participating centres in Spain. The indications for liver transplantation are shown in Table 1. Patients were followed up for a mean period of 309 days posttransplantation. The most frequent indication for liver transplantation was posthepatitic cirrhosis, particularly hepatitis C virus (HCV) cirrhosis (38 patients, 45 % of cases), associated with hepatocellular carcinoma in 11 patients. The second most frequent indication was alcoholic cirrhosis (n = 18; 21 %). Cholestatic diseases represented only 11 % of cases. Patients undergoing retransplantation (n = 3) and with fulminant hepatitis (n = 3) were also included. An important number of transplant recipients had clinically significant preoperative risk factors: 6 had renal dysfunction (7.1 %), 8 had diabetes (9.5 %) and 5 were suffering from arterial hypertension (6 %). The mean donor age was 40.5 years and the mean cold ischaemia time was 8.6 h.

Withdrawal from the study

Twenty-seven of the 84 patients (32.1 %) were withdrawn during the course of the study: 1 related to rejec-

Table 1 Primary indications for liver transplantation (HCV Hepatitis C virus)

Indication	Number
Cirrhosis	63
Posthepatitis C	28
Posthepatitis B	3
Posthepatitis B + D	1
Alcoholic	18
Primary biliary	7
Secondary biliary	1
Cryptogenic	5
Hepatocellular carcinoma and cirrhosis	11
HCV	9
Non-viral	2
Primary sclerosing cholangitis	2
Fulminant hepatic failure	3
Retransplantation	3
Hepatic artery thrombosis	1
Chronic rejection + HCV	1
Hepatitis B with liver failure	1
Miscellaneous	2
Metabolic disease	1
Haemangioendothelioma	1

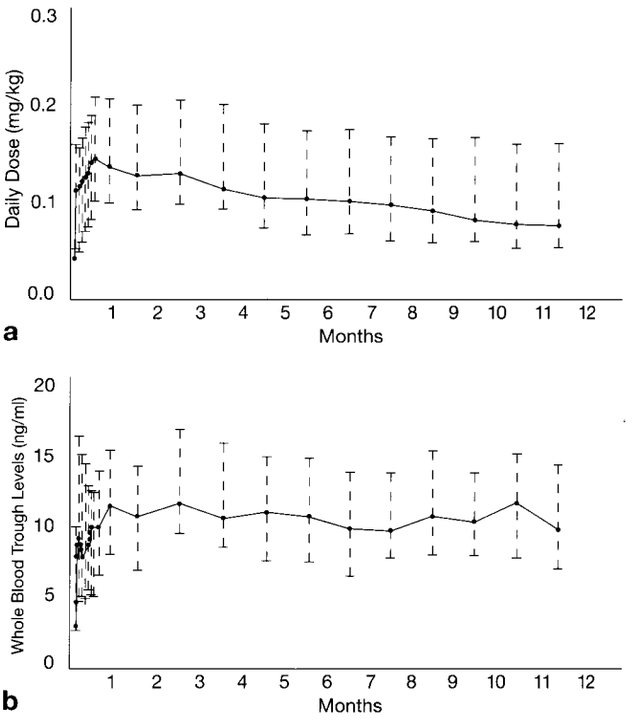

Fig. 1 Tacrolimus daily oral dose **(a)** and whole blood trough levels **(b)**. Graphs show median and quartiles

tion, 1 because of a temporary switch to cyclosporin, 3 required retransplantation and 13 (15.5%) died. The other 9 patient withdrawals (10.7%) were related to adverse events: abnormal kidney function ($n = 4$), neurotoxicity ($n = 2$), hypertension ($n = 1$), hyperglycaemia ($n = 1$) and lymphoma ($n = 1$). The patient with lymphoma is currently in complete remission and clinically well more than 1 year after liver transplantation after reintroduction of low-dose tacrolimus.

Tacrolimus dosage and whole blood concentrations

None of the patients received intravenous administration of tacrolimus during the study. The median oral dose of tacrolimus increased gradually over the first few weeks to a maximum dose of 0.145 mg/kg per day at week 3–4. The dose was subsequently decreased steadily, reaching a minimum of 0.076 mg/kg per day at 12 months (Fig. 1a). The proportion of patients with blood levels of tacrolimus above, below and within the therapeutic range during the first 2 weeks of treatment is shown in Table 2. By the end of the first week (day 7), levels were within the accepted therapeutic range (5–20 ng/ml) in almost 90% of patients. The proportion of patients with concentrations above the target range was highest within the first 2 days after surgery (16.2%), which was largely attributed to those patients with severe primary graft dysfunction (SGOT or SGPT > 3000 U/l) (Fig. 2). After the 2nd week post-transplantation, median blood levels of tacrolimus re-

Table 2 Dose and whole blood trough levels of tacrolimus

Day	Median dose (mg/kg per day)	Median levels (ng/ml)	Percentage of patients		
			< 5 ng/ml	5–20 ng/ml	> 20 ng/ml
1	0.103	< 5	47.5	44.2	8.2
2	0.104	7.95	22	61.8	16.2
3	0.104	8.45	25	61.8	13.2
4	0.107	8.65	14.5	77.6	7.9
5	0.109	8.45	13.2	84.2	2.6
6	0.114	7.9	14.8	82.7	2.5
7	0.117	7.6	9.6	87.7	2.7
14	0.144	10.05	1.5	93.9	4.5

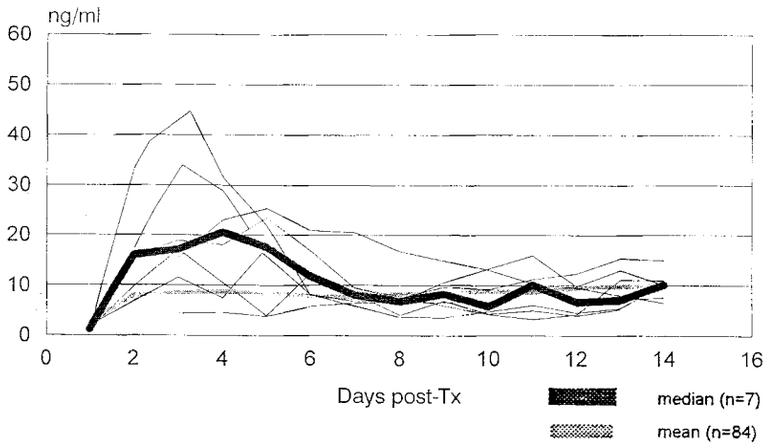

Fig. 2 Tacrolimus blood trough levels in seven patients with severe ischaemic injury (SGOT or SGPT > 3000 U/l)

mained fairly constant, reaching a maximum of 11.8 ng/ml over the remainder of the 12-month study period (Fig. 1 b).

Patient and graft survival

The Kaplan-Meier estimated rates of patient and graft survival were 90.5% and 89.3% at 2 months, 79.8% and 76.2% at 6 months, and 75.9% and 72.3% at 12 months, respectively (Fig. 3). Twenty deaths were reported (7 of them occurred after withdrawal) (Table 3). Eighteen of the deaths were not related to retransplantation, while 2 of the 5 patients who required retransplantation died, 1 from postanoxic encephalopathy and 1 from graft versus host disease. Eleven patients (13%) died during the first 3 months post-transplantation. These were either high-risk patients (two retransplantations, one hepatorenal syndrome and two diabetics) or patients who developed multiorgan failure due to graft dysfunction ($n = 4$). However, 2 deaths were related to the immunosuppressive treatment; 1 patient died from aspergillus pneumonia after being treated with corticosteroids and OKT3 for severe acute rejection, and another patient developed encephalopathy progressing to coma and died despite withdrawal of tacrolimus therapy. Nine of the 20 patient deaths occurred after 3 months. Infectious complications were the most frequent causes, 3 patients having severe recurrence of HCV infection, and another with AIDS transmitted by a blood transfusion during the liver transplantation procedure. Two deaths were related to malignancy, one recurrent hepatocellular carcinoma and one Kaposi's sarcoma of the liver. One patient with chronic rejection died from bilateral pneumonia.

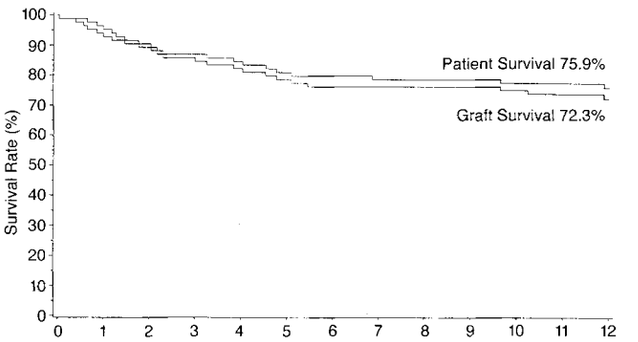

Fig. 3 One-year actuarial patient and graft survival (Kaplan-Meier method)

Rejection episodes

Forty-three patients (51.2%) experienced a total of 47 episodes of acute rejection (Table 4). Eight of the 47 episodes improved without antirejection therapy, although there was a need to increase the dose of tacrolimus in 2 patients. Thirty-five patients (41.7%) required treatment with corticosteroid boluses, 9 of which proved to be corticosteroid-resistant (10.7%) and required treatment with polyclonal or monoclonal antilymphocyte globulin. Two patients (2.4%) experienced refractory acute rejection and were considered treatment failures. One of these cases progressed to chronic rejection 35 days after the previous diagnosis of refractory acute rejection. Tacrolimus was discontinued and the patient died from liver failure and bilateral pneumonia. The other patient was treated with high-dose corticosteroids and OKT 3 and died from aspergillus pneumonia. Most episodes of acute rejection occurred during the 1st month post-transplantation, with none occurring after the 2nd month. During the 12 months of follow up, only 1 patient (previously mentioned) developed chronic rejection.

Table 3 Causes of death and retransplantation

Cause	Number
Early death (< 3 months)	11
Graft dysfunction, multiorgan failure	3
Hepatic artery thrombosis, sepsis	1
Renal insufficiency	1
Haemoperitoneum	2
Pulmonary hypertension	1
Encephalitis, coma	1
Acute rejection, aspergillus pneumonia	1
Graft dysfunction, retransplantation: anoxic encephalopathy	1
Late death (> 3 months)	9
Infections [CMV pneumonia (1), pulmonary nocardiosis (1), sepsis (1), AIDS bilateral pneumonia (1)]	4
Respiratory failure	1
GVH disease following retransplant	1
Recurrence of hepatocellular carcinoma	1
Kaposi's sarcoma	1
Chronic rejection, bilateral pneumonia	1
Indications for retransplantation	5
Primary non-function	1
Hepatic artery thrombosis	3
Ischaemic biliary stenosis	1

Table 4 Type of rejection

Rejection	Number of patients (n = 84)	Number of episodes
Acute	43 (51.2%)	47
Spontaneously resolving	8 (9.5%)	8
Corticosteroid-sensitive	28 (33.3%)	29
Corticosteroid-resistant	9 (10.7%)	10
Refractory	2 (2.4%)	2
Chronic	1 (1.2%)	1

Other immunosuppressive agents

The Kaplan-Meier estimates for the rate of patients on monotherapy was 0% at the end of month 2, 20.9% at the end of month 6 and 73.8% at the end of the 12-month period. The median time from liver transplantation to conversion to monotherapy was 8.5 months. Eight patients received azathioprine for a median duration of 9 days. Nine patients were treated for corticosteroid-resistant rejection with OKT3 for a median of 10 days and 2 patients received ATG therapy.

Infections

Seventy-one patients (84.5%) experienced 196 episodes of infection, most of which occurred during the first month after transplantation. Bacterial and viral infections were each documented in 38.8% of cases and 9.1% of patients had fungal infections (candida 7.1% and aspergillus 1.2%). Pneumonia (5.9%), urinary tract infection (9.5%) and sepsis (9.5%) were the most common bacterial infections. The incidence of cytomegalovirus (CMV) disease was quite low (9.5%), although CMV pneumonitis was the cause of death in 1 patient.

Safety analysis

The most frequently reported adverse events are shown in Table 5. Renal dysfunction was the main reason for tacrolimus dose reduction or interruption. However, the incidence of acute renal failure requiring haemodialysis was only 3.6% (3 patients). At 12 months, only 2 patients had serum creatinine values higher than 2 mg/dl. Diabetes mellitus was defined as the need for insulin to treat abnormal blood glucose after 1 month post-transplantation. Eight patients had pre-existing diabetes mellitus before transplantation. The overall incidence of diabetes during the study period was 33.3%. At the end of the study, 15.8% (9/57) of patients still required insulin. In 6 patients the dose of tacrolimus was reduced and was discontinued in 1 patient. Hypertension was the most frequently reported adverse event, being observed in 45.2% of patients. The dose of tacrolimus was reduced because of hypertension in 9 patients and was discontinued in 1 patient. At the end of the study, hypertension was ongoing in 14 patients (14/57 = 24.6%), 5 being diagnosed during the 1st month and the remaining after the 2nd month. Adverse events affecting the nervous system were reported in 52.4% of cases. Tremor was the most frequent complication, occurring in 44% of patients. The dose of tacrolimus was reduced in 11

Table 5 Safety analysis

Adverse event	Overall (n = 84)	First month (n = 84)	Month 2–12 (n = 74)	Dose reduction or interruption (n = 84)
Hypertension	38 (45.2%)	26 (31%)	26 (35.1%)	9 (10.7%)
Tremor	37 (44%)	20 (23.8%)	25 (33.8%)	12 (14.3%)
Diabetes mellitus	28 (33.3%)	6 (7.1%)	28 (37.8%)	6 (7.1%)
Diarrhoea	26 (31%)	15 (17.9%)	17 (23.0%)	7 (8.3%)
Nephrotoxicity	25 (29.8%)	15 (17.9%)	22 (29.7%)	19 (22.6%)
Headache	15 (17.9%)	6 (7.1%)	11 (14.9%)	–

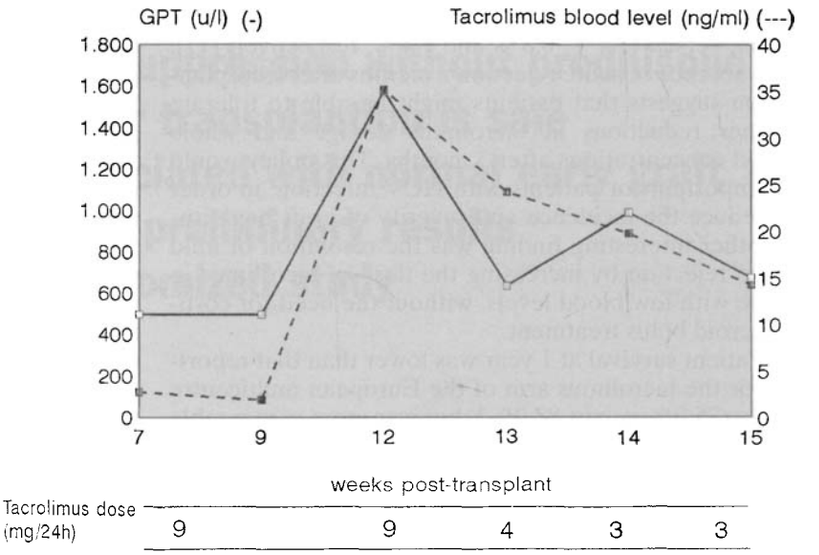

Fig. 4 Tacrolimus dosage and whole blood trough levels in a patient with recurrent HCV hepatitis

patients and temporarily discontinued in 1 patient. Dysarthria was documented in 8 patients (9.5%), convulsions in 4 patients (4.8%), paraesthesia in 4 patients (4.8%), delirium in 1 patient (1.2%) and coma in 1 patient (1.2%).

Of the 38 patients (45.2%) who had a primary diagnosis related to HCV infection, 21 (55.3%) had recurrence of hepatitis. Graft dysfunction caused by HCV recurrence resulted in an increase in blood levels of tacrolimus, which were frequently associated with drug toxicity, including diabetes, renal dysfunction, hypertension or tremor (Fig. 4). The dose of tacrolimus had to be decreased to avoid toxic levels, and the patients could usually be managed effectively on lower doses. At 1 year, the mean dose of tacrolimus in HCV-positive patients with recurrent hepatitis infection (16 patients) was 0.066 ± 0.058 mg/kg per day, which was significantly lower than the mean dose of the remaining 41 patients (0.103 ± 0.058 mg/kg per day) ($P < 0.01$). Comparing the outcome of the subgroup of patients with HCV infection with patients who had other types of end-stage liver disease, there were no differences in rejection rates, patient and graft survival, withdrawal rate or the type and incidence of infection after 1 year of follow up.

Discussion

The two large, multicentre, randomised studies performed in the USA and Europe, comparing tacrolimus to the optimal cyclosporin-based immunosuppressive protocol used in each study centre, demonstrated a significant reduction in the rates of acute and chronic rejection with tacrolimus therapy. However, this improved efficacy was shadowed by the more frequent occurrence of adverse events and toxicity in the tacrolimus arm. Following this experience, it became clear that optimisation of tacrolimus treatment was necessary. In the present study, tacrolimus was given orally at a low dose, with the aim of reducing the inherent side effects and toxicity associated with intravenous administration, and thus taking advantage of its bile-independent oral absorption while maintaining efficacy.

This study has shown that effective immunosuppressive therapy in liver transplantation can be obtained using low-dose, oral administration of tacrolimus. Intravenous administration was not necessary in any patient during the study. Initial oral administration resulted in attainment of therapeutic blood levels of tacrolimus very early after transplantation in most patients. Monitoring of tacrolimus whole blood trough levels is essential in order to adjust the dose where necessary, since toxic levels may occur in patients with initial poor graft function or in patients with recurrence of HCV infection resulting in impaired drug metabolism. The median dose of tacrolimus had to be increased during the 1st month after liver transplantation, but was then gradually reduced, particularly in patients with recurrent HCV infection. Most patients could be maintained at tacrolimus whole blood trough levels of around 10 ng/ml, and thus the recommended therapeutic range would probably be between 5 and 15 ng/ml. Another important advantage of tacrolimus treatment is the possibility of withdrawing corticosteroid therapy: a total of 73.8% of the patients were on tacrolimus monotherapy at the end of 1 year.

Efficacy was not affected by the use of low oral doses, with associated low initial trough levels of tacrolimus, since acute, refractory acute and chronic rejection rates in the Spanish study were comparable to those reported

in the European multicentre study (51.2%, 2.4% and 1.2%, versus 43.4%, 0.8% and 1.4%, respectively) [1]. The absence of acute rejection 2 months after transplantation suggests that patients might be able to tolerate further reductions in tacrolimus dosage and whole blood concentrations after 3 months. This policy would be important for patients with HCV infection, in order to reduce the incidence and severity of graft hepatitis. Another interesting finding was the resolution of mild acute rejection by increasing the dose of tacrolimus in those with low blood levels, without the need for corticosteroid bolus treatment.

Patient survival at 1 year was lower than that reported for the tacrolimus arm of the European multicentre study (75.9% versus 82.9%), but was more comparable to the patient survival rate in the cyclosporin arm (77.5%) and to other experiences reported by Spanish liver transplant programmes [3, 7]. Early mortality during the first 3 months was high, but was not related to the immunosuppressive protocol. This can be explained by the inclusion of high-risk patients in the study, including those undergoing retransplantation, those with fulminant hepatic failure, hepatocellular carcinoma or renal dysfunction, and recipients over 60 years of age (14.3%), plus the fact that the majority of graft recipients had viral infections (HCV and HBV) [9]. The retransplantation rate, however, was lower than that observed in other studies and the need for retransplantation was unrelated to the immunosuppressive therapy. CMV disease was uncommon, confirming previous reports that a significant reduction in CMV infection and disease could be achieved with tacrolimus immunosuppression [5]. This is probably related to a reduced need for corticosteroid bolus, OKT3 or polyclonal antilymphocyte globulin for the treatment of rejection.

One objective of this study was to determine whether low-dose, oral tacrolimus could reduce the incidence of adverse events. Withdrawal due to adverse events was 14.1% and 32% in the USA and European studies, respectively, mainly due to early nephrotoxicity and neurotoxicity, whereas withdrawal due to adverse events in the Spanish study was only 10.7%. Adverse events predominantly occurred during the 1st month in the USA and European studies, and were largely attributed to the administration of high intravenous doses of tacrolimus. In our study, adverse events were more frequent after the 2nd month, and were probably related to the increased toxicity in patients with recurrent HCV infection. Early nephrotoxicity was rare, and only three patients (3.6%) required haemodialysis compared with 10.3% in the USA study. There were no cases of newonsed diabetes in the early phase of the study. Tremor was the most frequently reported neurological adverse event. However, severe neurological problems were rare, leading to discontinuation of tacrolimus or withdrawal from the study in only one case. In conclusion, we have found that low-dose, oral tacrolimus provides effective immunosuppression in liver transplantation and is associated with a relatively low rate of adverse events.

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