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Influence of posttransplant time on dose and concentration of tacrolimus in liver transplant patients

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Abstract The dosage of tacrolimus (D), the trough blood concentrations (C) and the evolution of the D/C ratio were followed for 1 year after transplantation in so adult patients (38 males and 12 females) undergoing liver allograft. A total of 1489 samples were analysed by the IMx tacrolimus method. The overall median concentration was 11.27 ng/ml. During the 1st month the median of the tacrolimus levels was 8.4 ng/ml, and 73.1 % of the analysed samples were within the established therapeutic range. The median oral tacrolimus dose was progressively reduced from 0.12 mg/kg per day during the 1st month to 0.06 mg/kg per day at the end of studied period. A significant negative association was observed between the D/C ratio and the posttransplantation period ($r = -0.3892$; $P < 0.0001$). The median D/C ratio ranged from 0.0144 at 1st month to 0.0053 at 1 year. Significant D/C declines were observed after the 1st and 3rd months posttransplant. The decrease in corticosteroid doses and the increase in serum albumin may explain the reduction in clearance with time.

Key words Tacrolimus · Trough blood concentration · Liver transplant

Introduction

Previous clinical trials showed that initial short-term infusions of intravenous tacrolimus and initial oral doses of 0.3 mg/kg twice daily, with a therapeutic range between 10–25 ng/ml, led to a high incidence of toxicity [1, 2]. The aim of the Spanish multicentre liver transplant study [3] was to evaluate the clinical practicability of initial oral tacrolimus therapy at a low dose of 0.1 mg/kg per day, and to confirm a significantly reduced incidence of all adverse events. One-year follow up of the dosage and tacrolimus concentrations in liver transplant patients has been reported in order to assess the effect of the posttransplant period on the doses required to maintain tacrolimus trough blood concentrations in the therapeutic range.

Material and methods

Patients

Fifty patients (aged from 19 to 66 years) undergoing primary liver transplantation were evaluated for 1 year, in two centres, as part of the phase III a multicentre trial.

Immunosuppressive protocol

Tacrolimus therapy was initiated orally (0.1 mg/kg). Subsequent doses were adjusted on the basis of trough blood tacrolimus concentrations and according to the clinical status. Initial targets in the early posttransplant period were set between 5 and 15 ng/ml, and subsequently dropped to 5–10 ng/ml. Corticosteroids were used as concomitant immunosuppressive drugs.

Table 1 Median oral tacrolimus dose, median tacrolimus blood concentration and the ratio of the dose (D) to the concentration (C)

Months	Samples	Dose (mg/kg per day)	Concentration (ng/ml)	D/C)
0–1	792	0.12	8.4	0.0144
1–2	176	0.12	11.55	0.0098
2–3	97	0.10	11.8	0.0087
3–4	58	0.09	13.55	0.0061
4–5	42	0.09	12.45	0.0057
5–6	45	0.09	13.6	0.0057
7–12	279	0.06	10.1	0.0053

Blood sample collection and analysis

Blood specimens were drawn before the morning dose and blood tacrolimus levels were performed by the Abbott MEIA IMx method. Total bilirubin was determined by the Jendrassik-Groff method with a Hitachi 717 analyser.

Statistical analysis

Non-parametric correlation (Spearman) analysis was applied linking bilirubin and the posttransplant period with the ratio of the dosage of tacrolimus (D) to the trough blood concentration (C). The Wilcoxon and Kruskall-Wallis tests were used to determine statistical difference ($P < 0.05$) among groups.

Results

A total of 1489 blood samples were obtained. The median tacrolimus and bilirubin concentrations ($n = 728$) were 11.27 ng/ml and 1.2 mg/dl, respectively. During the 1st month posttransplant the median tacrolimus concentration was 8.4 ng/ml. From 792 blood samples measured, 118 levels (14.9%) were lower than 5 ng/ml, 579 (73.1%) were between 5 and 15 ng/ml and 95 (12%) were higher than 15 ng/ml. Samples were subdivided into intervals according to the posttransplant period. Median oral tacrolimus doses, concentrations and the D/C ratio over time are shown in Table 1.

The D/C values were significantly lower by the 2nd month posttransplant when compared with values during the 2st month (0.0098 vs 0.0144; $P < 0.001$). A continuous decline was observed until the 3rd month. After 90 days, the D/C ratio decreased significantly (0.0061 vs 0.0087; $P = 0.021$) and remained without further differences during the studied period.

Discussion

Initiating tacrolimus therapy at 0.1 mg/kg per day we found that 73.1% of tacrolimus blood levels were within the proposed therapeutic window (5–15 ng/ml). These results suggest that tacrolimus can be administered at a low dose of 0.1 mg/kg per day from the beginning of therapy. Obviously, the tacrolimus dosage must be adjusted on the basis of individual trough whole blood levels and in concordance with the clinical status of the patient.

The observed significant negative correlation between the D/C ratio of tacrolimus and the posttransplantation period could be explained as a decrease in clearance and/or an increase in oral bioavailability with time. Probably, in the 2st month, high doses of corticosteroids (inducers of tacrolimus' metabolism trough the cytochrome P450 3A4 enzyme) and hypoalbuminaemia (with high tacrolimus-free fraction) led to a significantly increased clearance of tacrolimus. We concluded that tacrolimus therapy could be initiated posttransplantation by the oral route at a dose of 0.1 mg/kg per day and that the median doses required to achieve blood therapeutic levels decrease significantly from the 2nd month.

References

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