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# Conversion from twice-daily to once-daily Tacrolimus administration in liver transplant patient: results of long term follow-up

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**Abstract. – OBJECTIVES: The aim of this study was to assess the long term effects of once-daily tacrolimus (OD-TAC) in a cohort of stable liver recipients converted from the twice daily tacrolimus (TD TAC), with a particular attention on the possible effects on renal function.**

**PATIENTS AND METHODS: Between September 2008 and September 2010 conversion from TD-TAC to OD-TAC was proposed in adult stable liver transplant recipients who were followed as outpatients in our Transplant centre. Conversion from TC-TAC to OD-TAC was based on a 1 mg: 1 mg proportion. Tacrolimus through levels, laboratory parameters, metabolic disorders and any adverse events were evaluated at 1, 3, 6, 12 and 24 months after conversion. Renal function was evaluated using creatinine plasma levels and estimated glomerular filtration rate (GFR) derived from the Modification of Diet in Renal Disease (MDRD). Analysis of variance and t test for paired data were utilised for the comparison of the results obtained at the scheduled controls.**

**RESULTS: Sixty-five patients were enrolled in the study (50 males, 15 females, mean age 59±8 years). Median time since liver transplant (LT) was 39 months (range: 6 to 83 months). All patients were followed for a minimum of 12 months. Ninety per cent of patients stabilized their blood levels within 45 days. Liver function, glucose and plasma lipids concentration and arterial blood pressure remained stable during the study. Renal function improved during the 24 months of follow-up. No adverse events or acute rejection episodes were recorded during the study.**

**CONCLUSIONS: Considering the advantage on patient compliance, the equivalent efficacy and the adequate safety of OD-TAC formulation may represent a useful option in liver transplant patients, with a possible advantage on renal function.**

*Key Words:*
Tacrolimus, Liver transplant recipients, Renal function.

## Introduction

In the last decades the development of new immunosuppressive drugs has contributed to a better control of the immune response against transplanted organs and has improved the long-term graft survival. Despite advances in immunosuppressive therapy, non-compliance to treatment remains a major problem in liver transplantation that leads to increased rejection episodes and graft loss[1]. Adherence seems to be significantly lower for the evening versus the morning dose[2] and inversely related to the prescribed number of pills[3].

The introduction of once daily tacrolimus (OD TAC) formulation, administered in the morning is associated with better adherence-to-therapy[4-5]. In a previous study we confirmed the once-daily administration as a useful tool for immunosuppressive therapy in liver transplant patients showing that steady-state exposure of tacrolimus TD formulation was equivalent to OD TAC after conversion[6]. The aim of this study was to assess efficacy, safety and renal function after two years of conversion from a twice daily tacrolimus regimen in a cohort of stable liver recipients.

## Patients and Methods

Between September 2008 and September 2010 conversion from TD-TAC to OD-TAC was proposed in adult stable liver transplant recipients who were followed as outpatients in our Transplant centre. All patients fulfilled the following inclusion criteria: being transplanted from at least 6 months, no acute rejection episode in the last 3 months and stable tacrolimus dosage in the



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last 3 months. Conversion from TD-TAC to OD-TAC was based on a 1 mg: 1 mg proportion. Blood immunosuppressant levels were evaluated at 1, 3, 6, 12 months and 24 months after conversion. Liver and renal function, lipid and glucose metabolism, arterial blood pressure and the occurrence of any adverse event were reported at each control visit. Renal function was evaluated using creatinine plasma levels and by using the estimated glomerular filtration rate (GFR) derived from the Modification of Diet in Renal Disease (MDRD) equation with six variables. Patients were defined as having renal dysfunction when MDRD was below 60 ml/min.

### Statistical Analysis

Results are expressed as mean ± SD. Analysis of variance and t test for paired data were utilised for the comparison of the results obtained at the scheduled controls.

## Results

Sixty-five patients were consecutively enrolled in the study (50 males, 15 females, mean age 59±8 years). Median time since liver transplant was 39 months (range: 6 to 83 months). Prior to entering the study, 13 of 65 (20%) and 25 of 65 (38%) patients were hypertensive and diabetic, respectively. All patients were followed for a minimum of 12 months. Dose adjustment was decided at each visit based on the variations of the immunosuppressant blood levels. Ninety per cent of patients stabilized their blood levels within 45 days and after 3 months from conversion no patients required further dose adjustment and the immunosuppressant serum level remained stable thereafter (Figure 1). Liver function, glucose and plasma lipids concentration as well as mean blood pressure remained stable during the 24 months follow up (Table I).

Renal function calculated by MDRD equation during the 24-months period after conversion showed a mild improvement (from 71 ± 21 ml/min at baseline to 82 ± 17 ml/min at 24 months; $p = 0.001$). Results were similar in the group of patients (18 pts) with a baseline renal dysfunction (CrCl < 60 ml/min). In this subgroup, renal function improved during follow-up from 51,2 ± 8 ml/min at baseline to 66,1 ± 11 ml/min after 24 months; ($p = 0.004$). No adverse events or acute rejection episodes were recorded during the study. In the remaining patients mean creatinine clearance and mean serum creatinine levels remained stable throughout the follow-up period.

## Discussion

The OD-TAC formulation has been proposed as a useful therapeutic option, which improves adherence to the immunosuppressive therapy compared to TD-TAC[4-5]. In the present study we extended our observation to a 24 months after conversion. We documented stable Tacrolimus serum level and dosage over two years follow-up, as also reported in recent studies[4-5,7]. None of the patients presented episodes of acute organ rejection. Metabolic parameters (serum glucose, lipid pattern) did not show significant changes. We observed a fair improvement of renal function during the observation period. The good renal function observed in the present study confirms the

**Table I.** Liver function, estimated GFR, glucose, lipids and blood pressure in liver transplant recipients at baseline and after the conversion from twice to once-daily tacrolimus.

| | Time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 3 | 6 | 12 | 24 | p |
| Aspartate aminotransferase (U/L) | 35 ± 29 | 29 ± 16 | 26 ± 17 | 24 ± 14 | 25 ± 13 | 0.6 |
| Alanine aminotransferase (U/L) | 38 ± 31 | 27 ± 14 | 25 ± 11 | 27 ± 13 | 24 ± 18 | 0.6 |
| Alkaline phosphatase (U/L) | 128 ± 138 | 92 ± 50 | 92 ± 50 | 90 ± 42 | 92 ± 40 | 0.09 |
| γ-glutamil transpeptidase (U/L) | 65 ± 83 | 40 ± 36 | 40 ± 30 | 39 ± 30 | 35 ± 30 | 0.3 |
| Total bilirubin (mg/dl) | 1.3 ± 0,9 | 1.2 ± 0,7 | 1.0 ± 0,5 | 1.2 ± 0,4 | 1.0 ± 0.3 | 0.4 |
| Estimated GFR (MDRD) (ml/min) | 71 ± 14 | 71 ± 21 | 75 ± 14 | 80 ± 18 | 82 ± 19 | 0.03 |
| Glucose (mg/dl) | 84 ± 28 | 81 ± 20 | 87 ± 27 | 80 ± 15 | 84 ± 12 | 0.9 |
| Total cholesterol (mg/dl) | 171 ± 44 | 168 ± 30 | 163 ± 38 | 164 ± 31 | 161 ± 34 | 0.5 |
| HDL cholesterol (mg/dl) | 49 ± 19 | 50 ± 16 | 51 ± 16 | 50 ± 14 | 55 ± 18 | 0.4 |
| Triglycerides (mg/dl) | 124 ± 74 | 127 ± 68 | 122 ± 87 | 101 ± 58 | 110 ± 60 | 0.3 |
| Systolic blood pressure (mmHg) | 124 ± 9,6 | 126 ± 16 | 130 ± 8 | 129 ± 12 | 130 ± 12 | 0.3 |
| Diastolic blood pressure (mmHg) | 76 ± 7 | 74 ± 8 | 75 ± 7 | 72 ± 6.5 | 70 ± 8 | 0.4 |

positive effect of OD TAC formulation already demonstrated by Sanko-Resmer et al[8] in a recent study performed on 112 patients who converted from TD TAC to OD TAC. In our study the amelioration of renal function was not associated with a reduction in TAC serum concentration (Figure 1). The improvement in renal function was also evident in the subgroup of eighteen patients with estimated creatinine clearance below 60 ml/min at baseline. The positive effects of OD TAC on renal function is an interesting result in liver transplant since renal failure is a significant cause of morbidity and mortality[11].

A criticism to our study is represented by the absence of a control group, this evidence did not allow us to draw definitive conclusions. With the regard to the mechanism involved it is possible that OD-TAC pharmacokinetic may have tempered its nephrotoxicity[8-9]. In fact a recent pharmacokinetic study report an average 11% lower $AUC_{0-24}$ in patients assuming OD-TAC vs TD-TAC. According to these authors in fact the slower access of OD TAC to CYP3A4 enzymes metabolism may prevent these enzymes from being overwhelmed by high drug concentration and reduced daily peaks. This more efficient metabolism decreases the bioavailabity of tacrolimus, without affecting its efficacy and safety[10].

## Conclusions

Considering the advantage on patients' compliance, the equivalent efficacy and the adequate safety OD-TAC formulation may represent a useful option in liver transplant patients, with a possible advantage on renal function.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

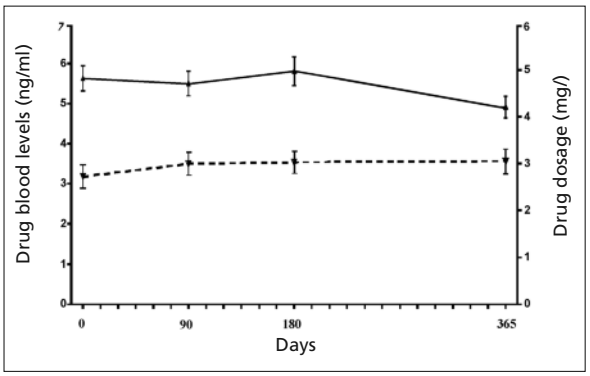


**Figure 1.** Tacrolimus blood levels (continuous line) and daily dosage (dotted lines) assumption after conversion from twice-daily to once-daily formulation.

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