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Experience of once daily tacrolimus individualised dosing through a bayesian approach in de novo liver transplant recipients

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Objectives

The aim is to analyze the efficacy and safety of once daily tacrolimus (TAC-OD) (Advagraf ®) individualised dosing aproach through a bayesian approach in de novo orthotopic liver transplant patients (OLT).

Methods

- **Design:** Retrospective observational study
- **Study period:** September 2012 – September 2016
- **Inclusion criteria:**
  - Adult OLT patients
  - Follow up: > 7 days
  - **Immunosupressive protocol (24h after OLT):**
    - TAC-OD (Advagraf ®): First day 0.15mg/kg po
    - Mycophenolate mofetil 1g/24h po
    - Steroids
    - Patients with renal dysfunction were treated with IL-2 receptor antagonists and tacrolimus (TAC) was delayed.
- **TAC-OD (Advagraf ®) analysis:**
  - Sample timing: trough every 24h in hospital and every outpatient visit
  - Tacrolimus concentration was analyzed using Indiko Plus® analyzer (ThermoFisher Scientific®)
- **TAC-OD (Advagraf ®) dose adjustment**
  - Population pharmacokinetic (PopPK) model was implemented in NONMEM v7.3
  - Calculation of the empirical bayesian estimates of the pharmacokinetic parameters
  - Dose adjustment of every blood withdrawn to:

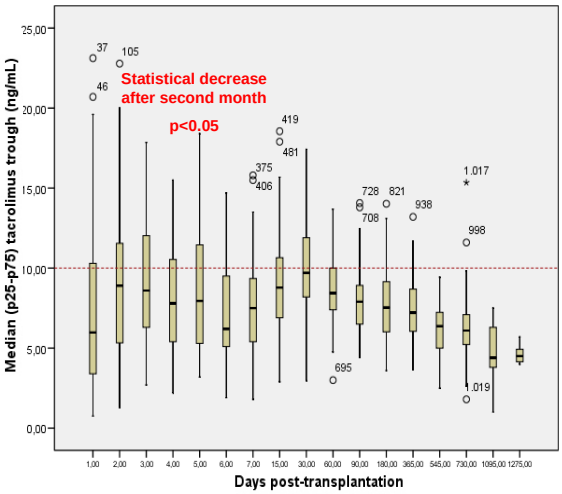
Tacrolimus target through	
First month OLT	8-10ng/mL
Thereafter	5-8ng/mL

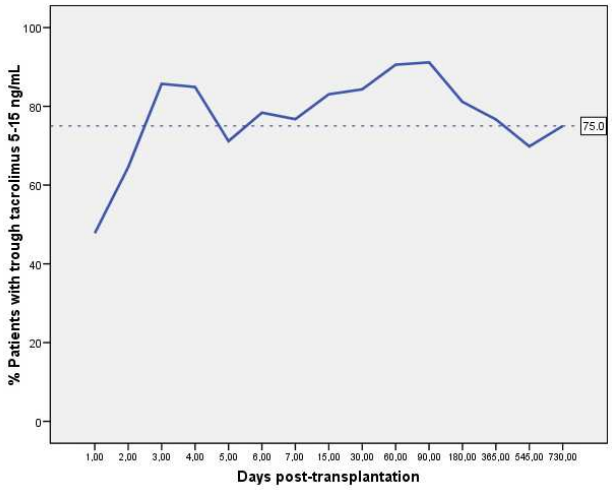
Variables	
Efficacy	Tacrolimus trough levels
	Hospital stay
	Survival
Safety	Serum creatinine (SCr)

Results

Demographics	Mean (CI 95%)
Patients (n)	99
Gender, male/female (%)	83.83/16.16
Age (years)	57.00(53.90-60.14)
Cause of liver disease	
Alcohol abuse	46.46
Hepatitis C virus (HCV)	31.31
Hepatitis B virus (HBV)	7.07
Other	15.15
MELD	15(12-18)

MELD: Model for End-stage Liver Disease





Efficacy and safety variables	
Hospital stay length, median (p25-p75)	4 days (3-6)
Patient Survival	
1 year	85%
2 years	83.4%
4 years	79.6%
Survival time, mean (IC95%)	41 months (37.6-44.4)
Serum creatinine, mean (IC95%) p>0.05	
Basal	1.11 mg/dL (1.17-1.45)
7 days after OLT	0.98 mg/dL (0.8-1.36)
4 years after OLT	1.11 mg/dL (0.99-1.24)

Discussion

Tacrolimus has a narrow therapeutic index with high pharmacokinetic variability. Monitoring TAC trough levels using a Bayesian population pharmacokinetic (popPK) model approach can be used to predict properly the dosage regimen of TAC-OD (Advagraf ®). With this methodology, we could shorter the time to achieve a target drug concentration in early postoperative days without worsen both clinical efficacy or toxicity. The major limitation of the study is that it uses retrospective data.

Conclusions

Our dosing protocol of TAC-OD based on bayesian methodology is feasible in routine clinical practice, target concentration was achieved at 72h in 75% of patients, and showing favorable outcomes in terms of survival and safety.