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

Más-Serrano P\textsuperscript{1}, Boquera Ferrer ML\textsuperscript{1}, Nalda-Molina R\textsuperscript{2}, Díaz González M\textsuperscript{3}, Rodríguez-Laiz G\textsuperscript{3}, Melgar P\textsuperscript{1}, Rodríguez Soler M\textsuperscript{1}, Carri
cer P\textsuperscript{1}, Liuis P\textsuperscript{3}, Selva Otaolaurruchi J\textsuperscript{1}\textsuperscript{1} General University Hospital of Alicante, Clinical Pharmacokinetic Unit. Department of Pharmacy, Alicante, Spain.
\textsuperscript{2} University of Miguel Hernandez, Engineering – Pharmacy and Pharmaceutics Division, San Juan de Alicante, Spain.
\textsuperscript{3} General University Hospital of Alicante, Hepatobiliary Surgery and Liver Transplantation Unit. Department of General Surgery, Alicante, Spain.

1 General University Hospital of Alicante, Clinical Pharmacokinetic Unit. Department of Pharmacy, Alicante, Spain.

Methods

\textbf{Objectives}

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

\textbf{Methods}

- **Design:** Retrospective observational study
- **Study period:** September 2012 – September 2016
- **Inclusion criteria:**
  - Adult OLT patients
  - Follow up: > 7 days
- **Immunosuppressive 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®)

\textbf{Results}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
\textbf{Demographics} & \textbf{Mean (CI 95\%)} \\
\hline
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) \\
\hline
\end{tabular}
\caption{Demographics of patients}
\end{table}

- **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:

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
\textbf{Tacrolimus target through} & \\
\hline
First month OLT & 8-10ng/mL \\
Thereafter & 5-8ng/mL \\
\hline
\end{tabular}
\caption{Tacrolimus target through}
\end{table}

- **Variables**
  - **Efficacy**
    - Tacrolimus trough levels
  - **Safety**
    - Serum creatinine (SCR)

\textbf{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.

\textbf{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.