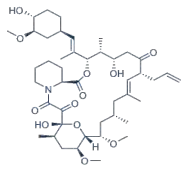
CASE REPORT NEWSLETTER

Issue 10

TACROLIMUS IN LIVER TRANSPLANTATION



AUTHORS: IVÁN BELTRÁ PICÓ Y PATRICIO MÁS SERRANO

PHARMACOLOGICAL GROUP: Immunosuppressants, calcineurin inhibitors.

MECHANISM OF ACTION: A competitive selective inhibitor of calcineurin leading to a calcium-dependent inhibition of T-cell signal transduction pathways.

THERAPEUTIC INDICATIONS:

As per the Data Sheet:

- Phrophylaxis of transplant rejection in kidney, liver or heart allograft recipients.
- Treatment of allograft rejection resistant to treatments with other immunosuppressants.

Off-label:

- Phrophylaxis of transplant rejection in allograft recipients.
- Immune conditions: nephrotic syndrome, lupus erythematosus, atopic dermatitis, psoriasis, aplasia, etc.

PHARMACEUTICAL FORMS:

- Concentrate for intravenous (IV) infusion: 5 mg/ml. .
- Granules for oral suspension: 0.2 and 1 mg.
- Immediate-release capsules*: 0.5; 1; 2 and 5 mg.
- Prolonged-release capsules* 0.5; 1; 2; 3 and 5 mg.
- Extended-release tablets (MeltDose): 0,75; 1 and 4 mg.
- Topic tracrolimus ointment 0.03; 0.1%

*Rapid-release capsules are administered twice daily. The rest of formulations are administered once daily.

POSOLOGY AS PER DATA SHEET:

High variability depending on the type of transplant, formulation used and the type of population:

Table 1. Tracrolimus dosing

Indication	Immediate and prolonged release IV infusion	Extended release *(MeltDose)*	Continuous IV infusion
Prophylaxis of rejection in **kidney transplant**	0.20-0.30 mg/kg/dday	0.17 mg/kg/day	Adults: 0.05-0.10 mg/kg/day Pediatrics: 0.075-0.10 mg/kg/day
Prophylaxis of rejection in **liver transplant**	0.10-0.20 mg/kg/day	0,11-0,13 mg/kg/day	Adults: 0.01-0.05 mg/kg/day Pediatrics: 0.05 mg/kg/day
Prophylaxis of rejection in **Heart transplant**	0.075 mg/kg/day	N/A	Adults: 0.01-0.02 mg/kg/day Pediatrics: 0.03-0.05 mg/kg/day
Prophylaxis of rejection of transplant in **pediatric patients**	0.30 mg/kg/day	N/A	N/A

ADVERSE REACTIONS:

Kidney failure (≥ 1/10); hypertension (≥ 1/10); Hyperglycemia (≥ 1/10); electrolyte abnormalities (≥ 1/100 a < 1/10); infections (≥ 1/10); cephalea (≥ 1/10); insomnia (≥ 1/10); tremor (≥ 1/10) and tinnitus ≥ 1/100 to < 1/10.

PHARMACOKINETICS (1):

Absorption: High variability and low water solubility (low absolute bioavailability (20-25% for immediate or prolonged release capsules and 40% for tablets with MeltDose® technology.

- Lower absorption: food, gastric motility (post-transplant and pre-systemic CYP3A-mediated metabolism. Use of prokinetic agents and laxatives concomitantly to retard capsules.

- Higher absorption: fasting, diarrhea (efflux pump inhibitors (P-glycoprotein); abnormal intestinal absorption and sublingual administration.

Absorbed throughout the gastrointestinal tract (differing depending on the formulation).

Tmax primarily depends on the formulation used:
(0.5-1; 2-3 or 6-7h, for immediate/prolonged/or Meltdose® extended release, respectively).

Distribution:

- In blood, extensive erythrocyte binding (blood:plasma ratio 15:1 [4-114]).
- In plasma, PU (99%), binding mainly to serum albumin and α-1-acid glycoprotein.
- Vd in whole blood: 0.9 L/Kg
- Vd in plasma: 30.1 L/Kg

Metabolism: widely metabolized in the liver by CYP3A4-CYP3A5>>>CYP3A7 and the intestinal wall.

Elimination:

- >95% metabolites excreted into the bile duct.
- <1% unchanged drug in urine, feces or bile.
- Cl in whole blood: 0.5 L/h/Kg
- Cl in plasma: 1.69 L/h/Kg
- $T_{1/2}$ = 4-41 h

- Higher clearance: young patients; [hematocrit ↓]; [albumin ↓]; shorter post-transplant time; low creatinine; CYP3A5* overexpression, and CYP3A4*1 homozygous carriers; interactions (corticosteroids; phenytoin; fenobarbital; carbamazepine; rifampicin or *Hypericum perforatum*).

- Lower clearance: underlying conditions (LF, diabetes…) and interactions (triazole antifungals, macrolides, diltiazem, proton pump inhibitors or protease inhibitors).

Population pharmacokinetic model:

Model 1 (2): Adult kidney transplant recipients receiving an immediate-release formulation twice daily or a prolonged-release formulation once daily:

- Two-compartmental model with first-order excretion. Covariates: CYP3A5, hematocrit and the tacrolimus formulation used.
- Pharmacokynetic parameters: Cl 21.6 L/h; Q = 82 L/h; V_c = 463 L; V_p = 329 L; K_{tr} = 3.39 h^{-1}
- Woillard JB, et al. Population pharmacokinetic model and Bayesian estimator for two tacrolimus formulations twice daily Prograf and once daily Advagraf. Br J Clin Pharmacol. 2011 Mar;71(3):391-402.

Model 2 (3): Stable liver transplant recipients receiving a first-order prolonged-release formulation once daily:

- Two-compartmental model with first-order lagged absorption and first-order elimination. Covariates: N/A.
- Cl= 4.21 L/h; Q = 14 L/h; V_c = 88.3 L; V_p = 145 L; F = 0.23 ka = 3.76 h^{-1}
- Moes DJ, et al. Population pharmacokinetics and pharmacogenetics of once daily tacrolimus formulation in stable liver transplant recipients. Eur J Clin Pharmacol. 2016 Feb;72(2):163-74.

TARGETED THERAPEUTIC WINDOW (4*):

Prophylaxis of liver transplant rejection	Prophylaxis of kidney transplant rejection
1. TAC+MMF/EVE+CC: • 0-1m: 6-10 ng/ml (A I**) • >1m: 5-8 ng/ml (A I**) 2. Monotherapy or induction: • 0-3m: 10-15 ng/ml (C1 II**) • 3m: 10-15 ng/ml (C1 II**) 3. Non-corticosteroid regimens: • 0-4 m 10-15 ng/ml (C1 II**) • > 4 m < 10 ng/ml 4. Pediatrics: • Sufficient evidence not available for recommendations to be issued.	1. Low immunological risk***: 1.1 IL-2R induction and TAC+MMF+CC: or Trough: 4-12 ng/ml (>7 ng/ml) (AI**) 1.2 thymoglobulin or IL-2R and TAC+EVE+CC: or 0-2m: Trough levels: 4–7 ng/ml (BII**) or >2m: Trough levels: 2–4 ng/ml (BII**) 2. AUC(0–12h) > 150 ng·h/ml ****(B II**) 3. Pediatrics: ● 0-2 m 10-20 ng/ml (C1 II**) ● >2 m 5-10 ng/ml

TAC, tacrolimus; MMF, mycophenolate mofetil; EVE, everolimus; CC, corticosteroids; IL-2R, interleukin 2 receptor blockers.
*The ranges provided in the table below are recommended in the second consensus document related to therapeutic monitoring of tacrolimus in blood.
**Grading System for Recommendations and Evidence Level Used in the Consensus Document.
***Therapeutic ranges could be higher for high-risk patients.
****Formulations administered twice daily. The range for AUC is derived from studies correlating Co with AUC in adult patients with different immunological risks and different immunosuppression schemes.

REASON FOR THERAPEUTIC DRUG MONITORING

- **Good correlation** of **tacrolimus** concentrations in blood with therapeutic **response** and toxicity.
- **High inter- and intra-individual variability in tacrolimus concentrations in blood.**
- **Narrow therapeutic range.**
- **Interactions** (CYP3A4/5/7, P-glycoprotein).
- NON-linear pharmacokinetics.
- Availability of the analytical technique.

CASE REPORT: MONITORING TACROLIMUS IN LIVER TRANSPLANT

CASE REPORT

We present the case of a male 70-year old liver transplant recipient that initiated treatment with triple immunosuppressive therapy including corticosteroids, mycophenolate and tacrolimus. Pharmacokinetic guided dosing of tacrolimus was performed.

THE PATIENT

Table 1. Medical history

A 70 year-old male

- No use of alcohol or other toxic substances.
- Urinary incontinence.
- Osteopenia.
- Severe COPD.
- Diagnosis of prostate cancer 6 years before. Treated with radiotherapy and surgery.
- HCV diagnosed 15 years before. Treated with interferon/RVB without response, without further follow-up.
- Hepatitis C-related liver cirrosis.
- Hepatitis C-related hepatocarcinoma.

Table 2. Previous treatment

- Solifenacin 5mg/24h PO.
- Calcifediol 0.266 ,g/30 days PO.
- Indacaterol + glycopyrronium 85/43 mcg/24h inhaled.

A 70 year-old man with abnormal liver biochemistry (AST: 137 U/L; ALT: 172; U/L; ALP: 155 U/L; Platelets: 136x10^3/lU) was referred for further investigation. The patient had active untreated HCV infection (HCV VC: 160,000 IU/ml) and liver cirrhosis. Prior to initiation of HCV treatment with sofosbuvir/velpatasvir, a space-occupying lesion was noted (45 mm) consistent with hepatocellular carcinoma. Following chemoembolization with complete response, sofosbuvir/velpatasvir therapy was initiated and a sustained response was achieved. After assessing the risk of recurrent prostate cancer and upon occurrence of a new space-occupying lesion in segment III measuring 12 mm, the patient was considered as a candidate for liver transplantation.

Pre-transplant study:

- Weight 91.4 kg; Height: 155 cm; BMI: 37.9 kg/m2. CA: rhythmic sounds without murmurs. Eupneic at rest. No neurologic deficit. No flapping. Edemas
- Biochemistry:
    - AST: 38 U/L; ALT: 34; U/L; GGTP: 33 UI/L; ALP: 100 U/L; Bt: 0.6 g/dl; Quick: 92%; INR: 1.06 s; PT: 6.7 g/dl Albumin: 3,5; Afp: 7.6; CKD-EPI >90 ml/min.

- MELD: 7, MELD Na^+: 9, Child-Pugh: A (6).
- Fibroscan: F4.
- Negative CMV (donor +) prophylaxis with valganciclovir 900 mg/24h PO (3 months).
- Negative toxoplasm (donor +) prophylaxis with cotrimoxazol 400/80 mg/24h PO (6 months).
- Negative quantiferon.

SOAP METHOD: Therapeutic monitoring of tacrolimus and dosage optimization

Clinical event	Therapeutic goal
Management of immunosuppression with tacrolimus in a liver transplant recipient. - Efficacy - Toxicity - Interactions	Optimization of immunosuppressive treatment by therapeutic monitoring of tacrolimus

Subjective-Objective

Table 3. Laboratory tests.											
	Urea	CRO	Bt	AST	ALT	GGT	ALP	PCR	HTC	GF	Mg
Day -1:	51	0.91	0.79	112	92	22	66	0.23	43.7	84.6	1.74
Day 0	49	0.97	1.19	**3220**	**2346**	52	48	2.62	34.3	76.7	2.32
Day +1	48	0.75	0.67	1314	1818	66	58	**16.2**	31.3	>90	2.47
Day +2	42	0.88	1.36	683	1432	254	142	9.43	27.8	86.6	2.65
Day +3	43	0.80	2.24	438	1165	651	233	5.01	31.0	>90	2.11
Day +5	46	1.5	**3.83**	366	637	697	274	4.73	34.4	46.5	1.41
Day +11	44	1.3	2.51	259	546	**792**	**428**	6.36	32.5	55	1.50
Day +14	47	1.3	2.32	230	501	621	350	3.9	32.8	55	1.56
Day +18	48	0.96	1.27	219	423	511	301	3.53	33.8	79.7	-
Day +28	51	0.92	0.86	47	135	112	121	0.86	34.6	84	1.56

Day 0, day of transplantation; Cr, creatinine; Bt, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HTC, hematocrit; GF, glomerular filtration rate; Mg, magnesium
Units: Urea, mg/dl; Cr, mg/dl; Bt, g/dl; AST, IU/L; ALT, IU/L; GGT, IU/L; ALP, IU/L; PCR, mg/dl; HTC, %; FG, ml/min; Mg, mg/dl

Table 4. Tacrolimus concentrations in blood.											
	Weight	Tacrolimus Dose	MMF Dose	CC Dose	C – trough	Bc-T2 h	Bc-T3 h	Bc-T5 h	Bc-T12h	$AUC_{0\,24h}$	Cl
Day 0	91.4	9	2000	160*	-	3.6	4.6	5.5	4.5	-	-
Day +1	90	10	2000	120*	2.2	10	14.3	18.4	-	166	54.3
Day +2	-	10	2000	80*	3.5	-	-	-	-	183	54.5
Day +3	91.7	15	2000	40	5.2	-	-	-	-	**288**	52.1
Day +5	90	15	2000	20	9.1	-	-	-	-	**342**	43.9
Day +11	-	13	2000	15	7.4	-	-	-	-	**283**	45.8
Day +14	87	13	2000	10	7.9	33	30	-	-	**327**	39.7
Day +18	83.3	10	2000	10	5.7	-	-	-	-	**260**	38.5
Day +28	-	9	2000	10	5.1	23.1	20.1	-	-	238	37.8

Units: Weight, kg; Dose, mg/day; Bc, ng/ml; AUC, ng·h/ml; Cl, L/h.
Bc, blood concentration; *, methylprednisolone (prednisone for the rest).

*S**ubjective-O**bjective-A**nalysis-P**lan*

On Day 0, transplantation was performed and triple immunosuppressive therapy was initiated with tacrolimus (Advagraf®) 9 mg/24 orally (0.1 mg/kg/day), plus mycophenolate mofetil 1000 mg/12h iv plus corticosteroids iv at decreasing doses. Prophylaxis with cotrimoxazol was concurrently initiated.

Day 0 (Hospitalization (H)):

S-O) CA: rhythmic sounds without murmurs. Eupneic at rest. No neurologic deficit. No flapping. Edemas.

A) From the first dose of tacrolimus, therapeutic drug monitoring was initiated as per protocol. Two consecutive blood curves were obtained (post-2h, post-4h, post-5h, post-12h and trough). Trough blood draw (C-trough) was performed early in the morning. In all hospitalized patients, tacrolimus dosing is established according to the results of the therapeutic monitoring performed that morning.

Day +1 (H):

S-O) The patetien ambulates without walking aids and tolerates oral intake. Lower limb edemas that extend to the hip.

A) Following the first curve (Graph 1) for a dose of 9 mg PO, the C-trough obtained was 2.2 ng/ml, with an estimated trough concentration prior to the following dose of 2.6 ng/ml and an $AUC_{0\text{-}24h}$ at steady state (AUCss) of 166 ng·h/ml. Graph 1 shows a lagged absorption that peaks (Cmax) at 5h vs. 2-3h in normal conditions for the prolonged-release formulation.

P) Since diuresis during surgery and in the past 24 hours was low and BT, GGT and ALP did not increase, the tacrolimus dose (Advagraf®) was up-titrated to 10 mg PO, and a new curve was obtained (estimated C-trough of 4.9 ng/ml).

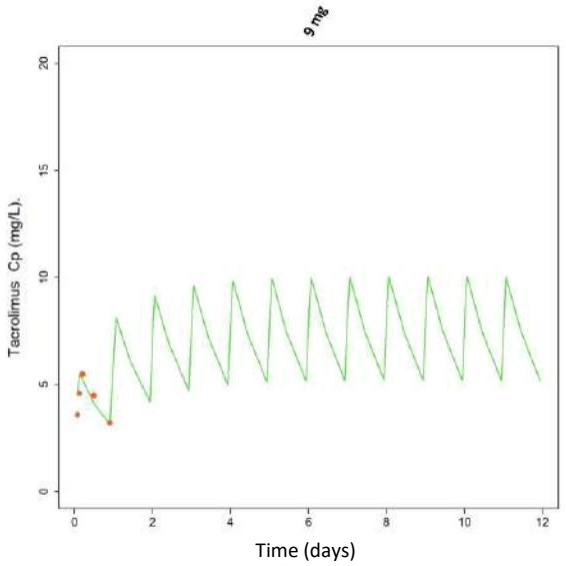
Day +2 (H):

S-O) Lower limb edemas improved (until the thigh). Hospital discharge.

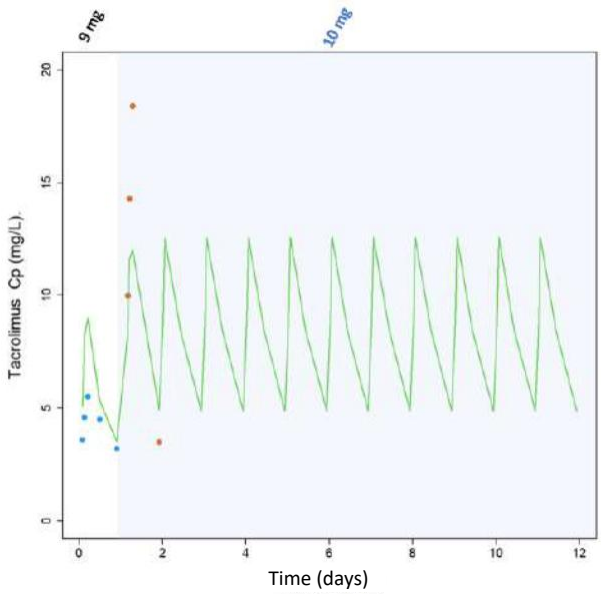
A) The second curve (Graph 2) was obtained for a dose of 10 mg, resulting in a trough concentration of 3.5 ng/ml and an AUCss of 183 ng·h/ml on Day +2. Low levels of ALT and AST persisted, with a slight increase in GGT and ALP. Despite the reduced hematocrit concentrations, the exposure profile observed in the second curve could be explained by changes occurring in the immediate post-transplant period. These changes may affect peristalsis and gastric voiding. Changes in hemoglobin values may also lead to increased tacrolimus absorption.

The absorption peak on Day +1 was significantly higher than the peak on Day +2, but with a very similar trough, thereby resulting in a higher AUCss.

P) In view of these results, added to C-trough values falling below the therapeutic range, it was decided to administer tacrolimus 15 mg PO, with an estimated C-trough at steady state (C-though$_{ss}$) of 5.4 ng/ml and an AUCss of 275 ng·h/ml within therapeutic range. Prophylaxis of CMV was initiated with valganciclovir 900 mg/24h PO. Prednisone 40 mg/24h PO at decreasing doses was maintained. The patient was discharged and referred to the Liver Transplant Outpatient Unit the following day.



Graph 1. Curve after the first dose of tacrolimus (9mg).



Graph 2. Curve after the second dose of tacrolimus (10mg).

Day +3 (Outpatient U.):

S-O) In good general condition (BEG). Good healing. Lower limb edemas.

A) We obtained an early C-trough (post-17h) of 5.2 ng/ml and an estimated AUCss of 288 ng·h/ml. With the same tacrolimus dose (Advagraf®) of 15 mg/24 h PO, the C-trough$_{ss}$ was estimated to be 8.4 with an AUCss of 341 ng·h/ml. GGT and ALP kept increasing, with preserved kidney function.

P) Although AUCss exceeded the therapeutic target (300 ng·h/ml), as the at steady state had not been reached and liver enzymes (ALP and GGT) were increasing, we maintained the current tacrolimus dose of 15 mg/24h PO, along with prednisone 20 mg PO at decreasing doses until the following monitoring.

Day +5 (Outpatient U.):

S-O) Good healing. Edemas at the level of the ankles. Moderate upper limb tremor.

A) The C-trough was 9.1 ng/ml with an estimated AUCss of 342 ng·h/ml. The C-trough was higher than on Day +3 due to the 3.5-increase in the hematocrit, concurrently to a reduced inductive effect following down-titration of corticosteroid dose.

Creatinine increased due to tacrolimus nephrotoxicity resulting from supratherapeutic exposure to tacrolimus (AUCss >300 ng·h/mL). GGT and ALP remained stable with respect to Day +3. Mild hypomagnesemia was noted. The patient exhibited hand tremor.

P) As liver function improved and kidney function worsened, tacrolimus dose was reduced to 13 mg/24h PO. The C-trough$_{ss}$ was estimated to be 7.3 ng/mL with an AUCss of 296 ng·h/ml. Down-titration continued and prednisone dose was reduced to 15 mg/24h PO. Magnesium supplementation with 53 mg 2-2-2 PO was initiated.

Day +11 (Outpatient U.):

S-O) No edemas. Upper limb tremor (hands) Liver doppler* was requested to study the elevation of liver enzymes.

* Liver Doppler ultrasound: this study is aimed at evaluating flow in the three main hepatic vessels (hepatic artery, vena porta and hepatic veins). This scan is used to screen for a possible thrombosis or anastomotic stenosis.

A) Six days after the last monitoring visit, a C-trough of 7.4 ng/ml and an AUCss of 283 ng·h/ml were obtained. Kidney function had increased slightly. Although GGT had increased slightly with respect to the previous monitoring, it was expected to decrease after the current GGT and ALT plateau period. Hand tremor persisted.

P) As kidney function improved and liver function stabilized, it was decided to maintain the tacrolimus dose of 13 mg/24 h PO. In the next monitoring visit, a new abbreviated tacrolimus curve was requested to assess actual patient exposure. Prednisone was down-titrated to 10 mg/24h PO. This dose was planned to be maintained for 3 months if the patient remained clinically stable. Magnesimum supplementation was maintained.

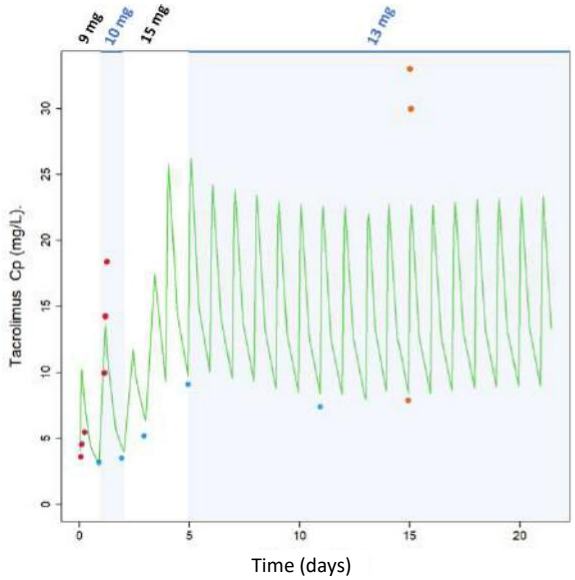
Day +14 (CExt.):

S-O) The general condition of the patient had improved. Hand tremor persisted. No edemas. US scan was normal*.

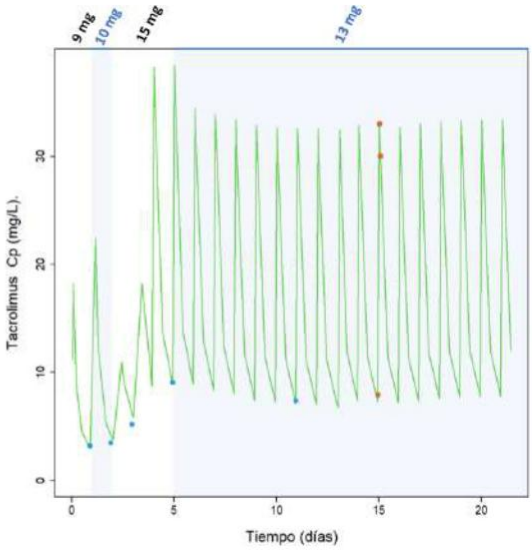
*US: liver was normal in appearance. The vena porta was patent. The hepatic artery was patent. The suprahepatic veins were patent. No intraperitoneal free fluid.

A) C-trough was 7.9 ng/ml. Graph 3 shows that concentration estimates at 2 and 3 hours post-administration were inaccurate. Moreover, Tmax passed from being reached at 5 hours in the immediate post-transplant period to being reached at 2 hours 14 days after transplantation. This could be due to restored peristalsis, continuous movement of the patient around the house and, in general, to the performance of daily living activities by the patient 14 days after surgery. To improve the accuracy of estimates and reflect the actual status of the patient, concentrations other than the C-trough values were removed from the two initial curves. As a result, the estimates of the third curve improved (graph 4, orange dots).

Following curve adjustment, the estimated AUCss was 327 ng·h/ml. Kidney function did not improve, as values keep below baseline ones. However, liver enzymes were decreasing. Tremor persisted.



Graph 3. Third tacrolimus curve (13 mg)



Graph 4. Third tacrolimus curve (13 mg), curves 1 and 2. were excluded

Day +18 (Outpatient U.):

S-O) In good general condition. No edemas. No temblor

A) C-trough was estimated to be 5.7 ng/ml and AUCss 260 ng·h/ml. Liver enzymes continued decreasing and kidney function returned to normal.

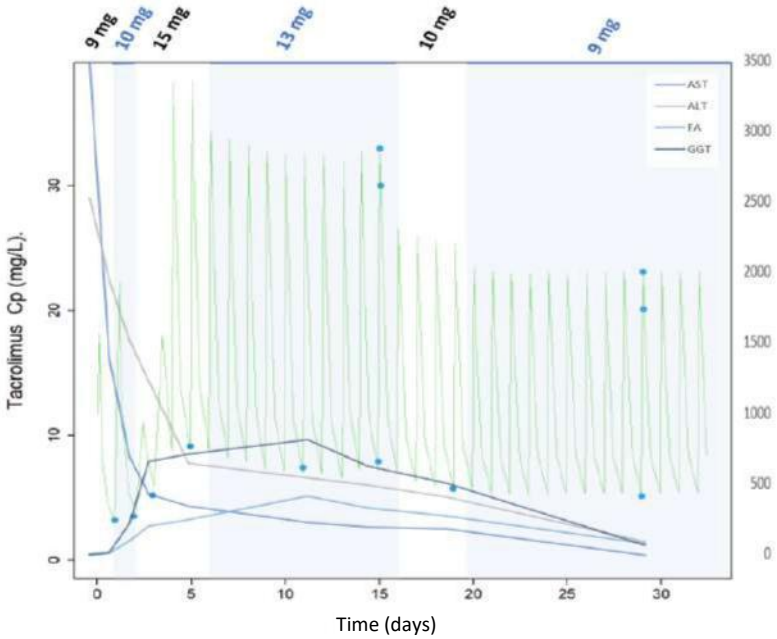
P) Since liver enzymes and kidney function improved significantly, the tacrolimus dose was down-titrated to (Advagraf®) 9 mg/24h PO, with an estimated C-trough$_{ss}$ of 5 ng/ml and an AUCss of 234 ng·h/ml. An abbreviated curve was requested for the 1-month post-transplant visit.

Day +28 (Outpatient U.):

S-O) No edemas. No tremor.

A) According to the abbreviated curve, the C-trough was 5.1 ng/ml with an AUCss of 238 ng·h/ml. Although the C-trough was below the target therapeutic range the first month post-transplant, exposure as per the AUC was within the target range. Kidney function remained stable and liver enzymes were close to normal limits.

P) The patient was receiving the same tacrolimus regimen (Advagraf®) of 9 mg/24h PO, MMF and prednisone, along with magnesium supplementation.



Graph 5. Changes in pharmacokinetics and biochemistry during the first month post-transplant.

Monitoring

During the post-transplant period, close monitoring of the efficacy and toxicity of tacrolimus was performed, with a special focus placed on nephrotoxicity, neurotoxicity and hypomagnesemia. Following transplantation, ALT and AST usually increase due to cytolysis after surgery, followed by an elevation of BT, GGT and ALP (see Graph 5). Levels of enzymes are not static, and their elevation and decrease kinetics should be correctly interpreted. Whereas levels of GGT increased by 300 IU between Day +2 and +3, they only increased by 50 IU between Day +3 and Day +5. This difference indicates that the GGT increase rate is slowing and close to reach the elevation plateau. Therefore, up-titration of the dose is not necessary. For this reason, the dose of tacrolimus was reduced on Day +5, although GGT had increased with respect to the previous control.

Another important factor to be considered during the therapeutic monitoring of tacrolimus is maintaining an adequate efficacy-toxicity balance. Hence, if tacrolimus concentration is increased to reduce the risk of rejection, the risk of severe adverse reactions increases, including the development of tumors. In the case presented, the correlation between C-trough and AUC was not always adequate, and total exposure to the drug was occasionally elevated, although the C-trough was within the targeted therapeutic window. Indeed, nephrotoxicity was noted on Day +5, possibly caused by a high tacrolimus exposure exceeding 300 ng·h/ml, although the C-trough was within therapeutic range. That day, the patient started to experience neurological toxicity, manifested in the form of upper limb tremor and hypomagnesemia. Both, nephrotoxicity and neurotoxicity, especially hand tremor, can be reversed by reducing tacrolimus exposure. In this case, these abnormalities disappeared when exposure decreased to < 300 ng·h/ml.

*D*iscussion

Table 5. Therapeutic targets in liver transplantation.					
	1 month	3 months	6 months	9 months	12 months
Tacrolimus	C-trough: 6-10 ng/ml AUC_{0-24h}:250-300 ng·h/ml	C-trough: 5-8 ng/ml AUC_{0-24h}: <250 ng·h/ml			
Prednisone	10 mg/day		5 mg/day	Withdrawal	
MMF	AUC_{0-12h}: 30-60				Down-titration to withdrawal

Therapeutic monitoring of tacrolimus in solid organ transplantation has demonstrated to be useful and effective in optimizing immunosuppressive therapy in this population (4).
This case highlights the need for continuous dose adjustments to maintain an adequate tacrolimus concentration in blood, according to the clinical course of the patient.

Tacrolimus may interact with drugs or herbs affecting CYP3A4/5/7 or the P-glycoprotein. Therefore, the use of this agent requires close monitoring. Liver metabolism inhibitors may reduce tacrolimus clearance. As a result, tacrolimus concentration in blood and the risk of toxicity increases significantly. Relevant drug interactions include triazole antifungals, macrolides, diltiazem, proton pump inhibitors, or certain antivirals used in the treatment of HIV or HCV. Drugs that may increase tacrolimus clearance, reduce its concentration and increase the risk of rejection include corticosteroids, phenytoin, phenobarbital, carbamazepine or rifampin, to name a few. The combination of tacrolimus with other nephrotoxic drugs may increase the risk of tacrolimus-related nephrotoxicity. Another key aspect is the administration of tacrolimus with meals, especially fat-rich meals, which reduce its absorption rate and bioavailability. Hence, it is recommended to administer tacrolimus on an empty stomach (4). On another note, pharmaceutical validation of concomitant treatments is crucial for detecting potential drug interactions. In case a potential interaction is detected, the pharmacist may suggest another option, if available. This way, interactions can be foreseen and managed by reducing or increasing tacrolimus dose.

Liver transplant is a major surgical procedure that may affect drug absorption during the immediate post-transplant period. Bioavailability increases over the first days post-transplant (5) due to reduced peristalsis. As a result, the residence time of the drug in the digestive tract increases, which affects drugs with a low clearance, such as tacrolimus.

Although AUC is the PK/PD index that best correlates with tacrolimus effectivity/toxicity, C-though is most frequently used in clinical practice. This is due to the difficulty in obtaining plasma concentration curves to characterize correct exposure in ambulatory patients. Different AUC ranges have been suggested as a function of time and the targeted C-though. However, the correlation between AUC and C-though varies throughout the first 12 months post-transplant due to the apparent reduction of tacrolimus clearance during that period (4).

During the first month post-transplant, the risk of rejection is higher and adequate immunosuppression becomes crucial. In this period, the target C-trough is higher than in the following period. As a result, the risk of toxicity increases and closer monitoring is needed. This is due to the fact that the transplanted organ has a higher level of immunogenicity during the immediate post-transplant period and progressively generates tolerance over time. The objective is to reach effective tacrolimus concentrations (C-trough 6-10 ng/ml and AUCss: 250-300 ng·h/ml during the first month). In our center, the therapeutic drug monitoring protocol is activated from the first dose without waiting for concentrations to reach the steady state. Liver transplantation surgery is included in the fast-track pathway of our Center (6), by which patients receive early discharge. An individualized monitoring of pharmacokinetics is essential for patients to be discharged home with the optimal dose. For such purpose, blood samples are drawn after the first dose to obtain two consecutive curves (Day 0 – post-2h, post-3h, post-5h, post-12h and trough concentration). Curves are used to estimate the volume of distribution and clearance and obtain a more accurate picture of the Cmax and Tmax. As a result, more precise AUC estimates are obtained. The administration of tacrolimus in inpatients is not initiated until the hospital pharmacist has validated it throughout the morning. Then, the patient is seen twice weekly in the Outpatient Liver Transplant Unit for the two first weeks post-transplant. In each visit, monitoring of C-trough values is performed and abbreviated curves are obtained (C-though, T2 and T3) at 7, 15, 30, 90, 180 and 365 days. In the case of ambulatory patients, medication is administered after the blood draw. The following day, tacrolimus dosing is adjusted. The use of a population pharmacokinetic model with an optimal predictive power, added to Bayesian estimates help obtain an accurate, individualized estimate of patient pharmacokinetics.

Then, simulations are used for an individualized dose adjustment. This method is useful for estimating the trough concentration at steady state at a given dose when the concentration has not yet reached the steady state. It also helps predict changes in clearance following the administration of packed RBCs in patients with anemia.

Later, the apparent clearance of tacrolimus progressively changes throughout the post-transplant period. A few days after transplantation, concentrations peak to progressively decrease later. The initial increase in clearance results from the induction effect of corticosteroids on CYP3A4 (7); other factors include low hematocrit values distinctive of the immediate post-transplant period. After two weeks post-transplant, tacrolimus clearance decreases. Clearance diminishes when anemia improves, tacrolimus retention increases (blood:plasma ratio 15-1), and corticosteroids are withdrawn (5, 8). Then, tacrolimus dosage needs to be reduced to reach similar targeted concentrations.

Finally, the high inter- and intra-individual variability in the pharmacokinetics of tacrolimus may generate dissociation between C-trough values and AUCs. Therefore, the two parameters and their correlation should be considered when adjusting the dose of tacrolimus.

Conclusions

Estimating individual pharmacokinetics using the Bayesian approach and an adequate population model is the most accurate and precise method for adjusting tacrolimus dosage in a patient.

The use of abbreviated curves facilitates the characterization of individual pharmacokinetic parameters (RV and Cl). Most importantly, they help estimate total exposure more accurately (AUC).

At specific time points during the first year post-transplant, it is necessary to use abbreviated curves for an accurate AUC estimation, as pharmacokinetics vary significantly over (elevated intra-individual variability).

REFERENCES

1. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet. 2004;43(10):623-53.

2. Woillard JB, de Winter BC, Kamar N, Marquet P, Rostaing L, Rousseau A. Population pharmacokinetic model and Bayesian estimator for two tacrolimus formulations--twice daily Prograf and once daily Advagraf. Br J Clin Pharmacol. 2011;71(3):391-402.

3. Moes DJ, van der Bent SA, Swen JJ, van der Straaten T, Inderson A, Olofsen E, et al. Population pharmacokinetics and pharmacogenetics of once daily tacrolimus formulation in stable liver transplant recipients. Eur J Clin Pharmacol. 2016;72(2):163-74.

4. Brunet M, van Gelder T, Asberg A, Haufroid V, Hesselink DA, Langman L, et al. Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report. Ther Drug Monit. 2019;41(3):261-307.

5. Storset E, Holford N, Midtvedt K, Bremer S, Bergan S, Asberg A. Importance of hematocrit for a tacrolimus target concentration strategy. Eur J Clin Pharmacol. 2014;70(1):65-77.

6. Rodriguez-Laiz GP, Melgar-Requena P, Alcazar-Lopez CF, Franco-Campello M, Villodre-Tudela C, Pascual-Bartolome S, et al. Fast-Track Liver Transplantation: Six-year Prospective Cohort Study with an Enhanced Recovery Afer Surgery (ERAS) Protocol. World J Surg. 2021;45(5):1262-71.

7. Antignac M, Barrou B, Farinotti R, Lechat P, Urien S. Population pharmacokinetics and bioavailability of tacrolimus in kidney transplant patients. Br J Clin Pharmacol. 2007;64(6):750-7.

8. de Jonge H, Vanhove T, de Loor H, Verbeke K, Kuypers DR. Progressive decline in tacrolimus clearance afer renal transplantation is partially explained by decreasing CYP3A4 activity and increasing haematocrit. Br J Clin Pharmacol. 2015;80(3):548-59.

Edited by: Grupo de Farmacocinética de la Sociedad Española de Farmacia Hospitalaria C/ Serrano, 40. 28001 Madrid
Tel: +34 91 571 44 87 Fax: +34 91 571 45 86
Email: sefh@sefh.es
Web: http://www.sefh.es
ISSN: 2697-083X