Effect of Direct Acting Antivirals on the Pharmacokinetics of Calcineurin Inhibitors

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Abstract

Background: Severe hepatitis C virus (HCV) recurrence affects post-transplant survival in HCV infected patients. We describe the effect of sofosbuvir-based anti-HCV therapy on disposition of anti-calcineurin immunosuppressive drugs.
Methods: Liver transplant patients (pts) with severe HCV recurrence who signed the informed consent were included in the ANRS CO23 CUPILT cohort and their characteristics recorded. Immunosuppressive therapy backbone was either tacrolimus (TAC) or cyclosporine (CyA). They were treated according to HCV genotype with 2nd generation direct acting antivirals (DAA) including sofosbuvir (SOF) with either daclatasvir (DCV) +/- ribavirine (RBV) or simeprevir (SMV) at standard dosing. Predose blood samples were drawn before DAA initiation (D0) and at week4 (W4) after DAA initiation. Trough concentrations (Ct) of TAC or CyA at steady state were measured by quality controls validated assays (immunoassay or LC-MS/MS). Apparent clearance (Cl/F) of TAC or CyA was estimated from the ratio of the dose per intake over the trough concentration (as a surrogate of average concentration at steady state) times the time interval between 2 doses Cl/F= D/(Δt*Ct). W4/D0 geometric mean ratio (GMR) and 2-sided 90% CIs (CI90) were calculated for Cl/F and compared to the 0.80-1.25 bioequivalence range. Unless otherwise indicated, results are medians and ranges.
Results: Twenty three pts were on TAC and 12 on CyA. Characteristics at inclusion were age 57years (43, 81), weight 72kg (45, 106) and MELD score 9 (0, 26). HCV genotypes were G1 (25 pts), G2 (2 pts) and G4 (8 pts). On the 3 pts on antiretrovirals, one was on efavirenz (EFV) and 2 on raltegravir-based regimen combined with 2 nucleoside analogs. Pt on EFV has the highest TAC Cl/F. Creatinine clearance (MDRD equation) remained unchanged at W4 compared to D0. Cl/F of TAC and CyA at D0 and W4 are shown in the table below.
Conclusion: Despite wide interindividual variability on TAC or CyA Cl/F, our data show that most liver transplant pts have an increased Cl/F on DAAs, statistically significant for TAC, leading to a decrease in concentrations and likely warranting an increased dosing. All these liver transplant pts should be monitored closely at the time of DAA initiation and during follow-up. These results need to be confirmed in a larger cohort of pts as well as the identification of factors explaining such drug-drug interaction.

Background

- Severe hepatitis C virus (HCV) recurrence affects post-transplant survival in HCV infected patients.
- We describe the effect of sofosbuvir-based anti-HCV therapy on disposition of anti-calcineurin immunosuppressive drugs in liver transplant recipients included in the ANRS CO23 CUPILT (Compassionate Use of Protease Inhibitors in Viral C in Liver Transplantation) cohort.

Methods

Patients

- Age > 18 years-old
- Liver transplant patients included in the multicentric ANRS CO23 CUPILT cohort
- Hepatitis C virus (HCV) infection before transplantation
- HCV recurrence with a detectable HCV RNA before enrollment in cohort
- 34 patients included in this study; among them 3 HIV coinfected

Treatment

- Immunosuppressive therapy: Calcineurine Inhibitors (CNI) as backbone. Tacrolimus BID or QD (TAC) or cyclosporine BID (CyA) were selected at center choice and dosing optimized to reach blood levels within the target range depending on time post transplantation
- Direct Acting Antivirals (DAAs): Sofosbuvir (SOF) 400 mg QD with either Daclatasvir (DCV) 60 mg QD (or 90 mg QD for patient on efavirenz) +/- Ribavirine (RBV) or SOF + Simeprevir (SMV) 150 mg QD, depending on drug availability and HCV genotype
- Antiretroviral therapy at investigator choice (1 patient on efavirenz and 2 on raltegravir-based regimen combined with 2 nucleoside analogs)

Sample collections and assays

- Predose blood samples were drawn for TAC/CyA assay, before DAA initiation (D0) and at week 4 (W4) after DAA initiation
- 1 patient non included from analysis since abstract submission for timing deviation
- Predose trough concentrations (C0) of TAC or CyA at steady state were measured by quality controls validated assays (immunoassay or LC-MS/MS) in each clinical center

Pharmacokinetic and statistical analyses

- Apparent clearance (Cl/F) of TAC or CyA was estimated from the equation Cl/F=D/(Δt*C0) assuming that C0 is close to the average concentration at steady state
- W4/D0 geometric mean ratio (GMR) and 2-sided 90% confidence interval (CI90) were calculated for Cl/F and compared to the 0.80-1.25 bioequivalence range
- Unless otherwise indicated, results are expressed as median and range

Results

Patient characteristics

	Tacrolimus (n=22)		Cyclosporine (n=12)	
Female/Male	5/17		2/10	
Age (years)	60 (43-81)		56 (45-63)	
	D0	**W4**	**D0**	**W4**
Weight (kg)	70 (45-93)	69 (47-93)	79 (58-106)	78 (53-105)
MELD Score	8 (0-19)	8 (0-26)	10 (5-17)	10 (5-15)
Creatinine clearance* (mL/min)	67 (19-162)	69 (15-164)	58 (41-159)	56 (40-132)

*MDRD equation

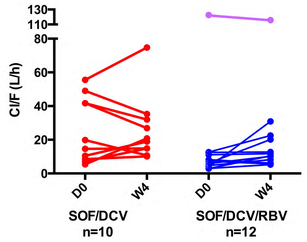
Treatment dosing at treatment initiation

Immunosuppressive drugs (µg/kg)			Ribavirin (mg/kg)
Tacrolimus		Cyclosporine	
QD (n=11)	BID (n=11)	BID (n=12)	(n=19)
19 (7-133)	8 (3-132)‡	760 (330-1610)	11 (5-15)

‡One patient on Modigraf

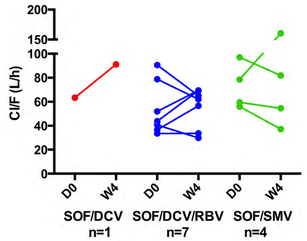
Estimated tacrolimus and cyclosporine Cl/F

	(n)	Tacrolimus Cl/F (L/h)	
		D0	W4
SOF/DCV	10	17 (5-56)	20 (10-75)
SOF/DCV/RBV	12	7 (3-123)	11 (5-116)

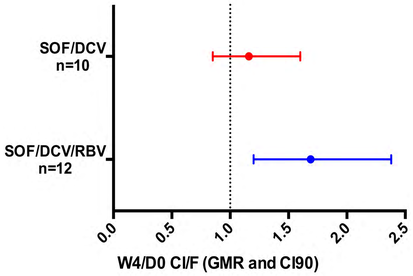


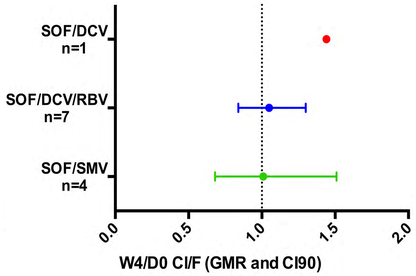
Patient on efavirenz (purple dots) has the highest TAC Cl/F (123 and 116 L/h).

	(n)	Cyclosporine Cl/F (L/h)	
		D0	W4
SOF/DCV	1	63	91
SOF/DCV/RBV	7	44 (34-91)	62 (30-69)
SOF/SMV	4	69 (56-97)	68 (37-161)



GMR and 90% CI for tacrolimus and cyclosporine Cl/F





Conclusions

- Despite wide interindividual variability on TAC or CyA Cl/F and small number of patients in each cohort, our data show that liver transplant patients have an increased TAC Cl/F after DAAs+RBV initiation, leading to a decrease in concentrations and warranting an increased dosing.
- All these liver transplant patients should be monitored closely at the time of DAAs initiation and during follow-up.
- Reasons for such TAC pharmacokinetic impairment at DAAs+RBV initiation need to be further investigated.

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