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& Clinical Toxicology

High intrapatient variability of tacrolimus exposure is associated with poorer outcomes after liver transplantation

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CONFLICTS OF INTEREST AND SOURCE OF FUNDING

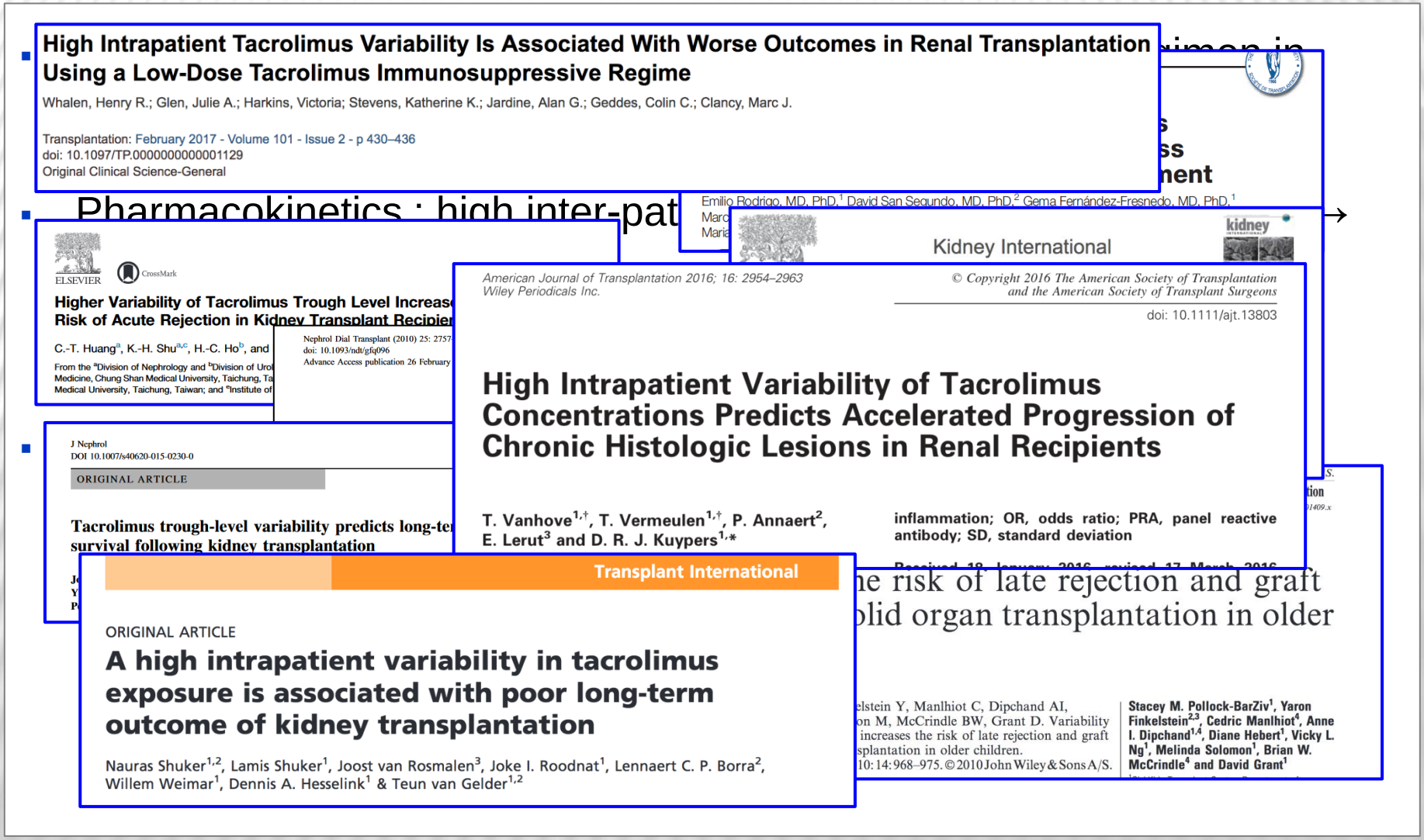
Dr Camille Tron (PharmD)

- None

BACKGROUND

- **Tacrolimus (TAC)** : Cornerstone of immunosuppressive regimen in organ transplantation
- Pharmacokinetics : high inter-patient AND **intra-patient variability** → unpredictable dose-response relationship → TDM of TAC trough concentration (C0)
- **Intra-patient variability (IPV) of TAC concentration :**
  - Associated with poorer outcomes in (“stable”) renal transplant recipients

BACKGROUND



High Intrapatient Tacrolimus Variability Is Associated With Worse Outcomes in Renal Transplantation Using a Low-Dose Tacrolimus Immunosuppressive Regime

Whalen, Henry R.; Glen, Julie A.; Harkins, Victoria; Stevens, Katherine K.; Jardine, Alan G.; Geddes, Colin C.; Clancy, Marc J.

Transplantation: February 2017 - Volume 101 - Issue 2 - p 430–436
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Original Clinical Science-General

Pharmacokinetics : high inter-pat

Emilio Rodrigo, MD, PhD,[1] David San Segundo, MD, PhD,[2] Gema Fernández-Fresnedo, MD, PhD,[1]

ELSEVIER CrossMark

Higher Variability of Tacrolimus Trough Level Increase Risk of Acute Rejection in Kidney Transplant Recipier

C.-T. Huang[a], K.-H. Shu[a,c], H.-C. Ho[b], and

From the [a]Division of Nephrology and [b]Division of Uro Medicine, Chung Shan Medical University, Taichung, Ta Medical University, Taichung, Taiwan; and [c]Institute of

Nephrol Dial Transplant (2010) 25: 2757
doi: 10.1093/ndt/gfq096
Advance Access publication 26 February

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High Intrapatient Variability of Tacrolimus Concentrations Predicts Accelerated Progression of Chronic Histologic Lesions in Renal Recipients

T. Vanhove[1,†], T. Vermeulen[1,†], P. Annaert[2], E. Lerut[3] and D. R. J. Kuypers[1,*]

inflammation; OR, odds ratio; PRA, panel reactive antibody; SD, standard deviation

J Nephrol
DOI 10.1007/s40620-015-0230-0

ORIGINAL ARTICLE

Tacrolimus trough-level variability predicts long-te survival following kidney transplantation

Transplant International

ORIGINAL ARTICLE

A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation

Nauras Shuker[1,2], Lamis Shuker[1], Joost van Rosmalen[3], Joke I. Roodnat[1], Lennaert C. P. Borra[2], Willem Weimar[1], Dennis A. Hesselink[1] & Teun van Gelder[1,2]

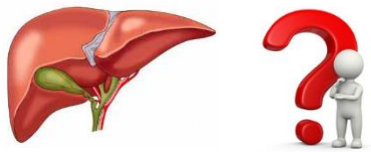
e risk of late rejection and graft
olid organ transplantation in older

elstein Y, Manlhiot C, Dipchand AI,
on M, McCrindle BW, Grant D. Variability
increases the risk of late rejection and graft
splantation in older children.
10: 14: 968–975. © 2010 John Wiley & Sons A/S.

Stacey M. Pollock-BarZiv[1], Yaron Finkelstein[2,3], Cedric Manlhiot[4], Anne I. Dipchand[1,4], Diane Hebert[1], Vicky L. Ng[1], Melinda Solomon[1], Brian W. McCrindle[4] and David Grant[1]

BACKGROUND

- **Tacrolimus (TAC)** : Cornerstone of immunosuppressive regimen in organ transplantation
- Pharmacokinetics : high inter-patient AND **intra-patient variability** → unpredictable dose-response relationship → TDM of TAC trough concentration (C0)
- **Intra-patient variability (IPV) of TAC concentration :**
  - Associated with poorer outcomes in (“stable”) renal transplant recipients
  - **Sparse data in liver transplantation**
    - Supelana et al. "Medication level variability index predicts rejection, possibly due to nonadherence, in adult liver transplant recipients." *Liver Transplantation* (2014)
    - Shemesh, et al. "The Medication Level Variability Index (MLVI) Predicts Poor Liver Transplant Outcomes: A Prospective Multi-Site Study." *American Journal of Transplantation* (2017).



OBJECTIVE

To evaluate the impact of IPV in TAC trough whole-blood concentrations in the early period after liver transplantation on graft and patient's outcomes.

METHODS

Study population :

- Adults liver transplant recipients in Rennes University Hospital (France)
- Between January 2002 and December 2014
- Retrospective analysis of data from a prospective database

Inclusion criteria:

- Patients with an orthotopic liver transplantation (OLT)
  - > 18 years old
  - Treated with TAC
- Started on POD 1 or 2 until at least POD 30

Exclusion criteria:

- Split graft
- Multiple organ transplantation
- Retransplantation
- Death before POD 15
- Ciclosporin or induction treatment
- TAC stopped before POD 30

POD= Post operative day

METHODS

Immunosuppressive regimen

Standardized immunosuppression

TAC / mycophenolate mofetil / short course of corticosteroids

Targeted therapeutic range:

trough concentration (C0) between 8 and 12 ng/ml.

IPV calculation

Coefficient of variation (CV)

Standard deviation (SD) of C0 / Mean TAC C0

Mean concentrations: from POD 8 to 30

2 groups:

low-CV group and high-CV group

Cut-off = 40% (third quartile of CV distribution)

Studied parameters

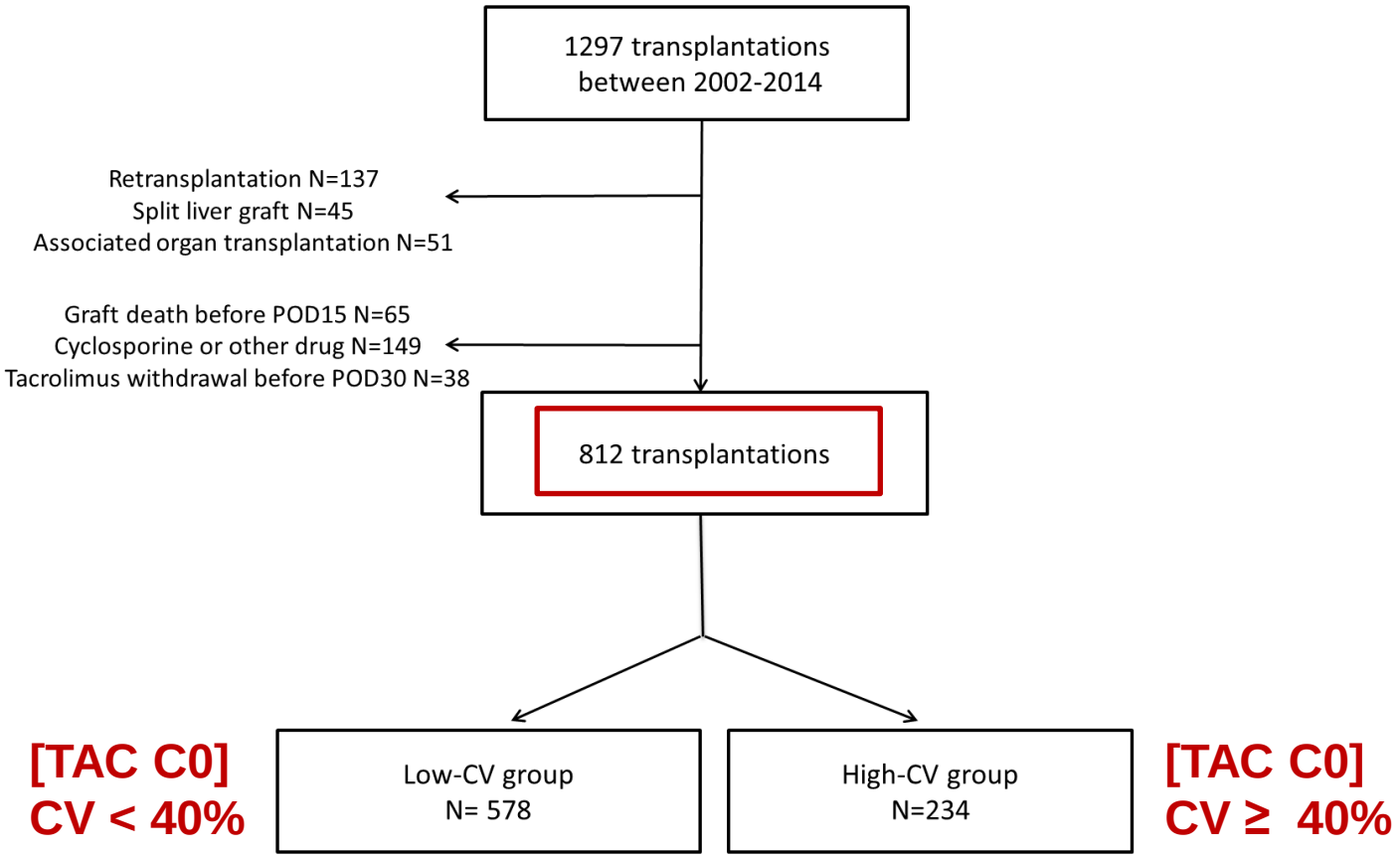
Patients characteristics	Post transplantation clinical and biological parameters
Gender , Age, BMI	TAC C0
Underlying liver disease and OLT indication	Early allograft dysfunction incidence
HCV infection	Acute rejection
Child Pugh class	ICU stay and Hospitalization duration
MELD score (median value)	Arterial complications and Biliary complications
Pre transplant CKD-EPI value	Dialysis CKD-EPI value (at POD30)
Cold ischemia time (min) Surgical duration (min) Bilioenteric anastomosis	Neurologic complications
Donor Gender, age and BMI	Cardio-vascular complications
Extended criteria donor graft	Patient and graft survival at 3 months, 12 months

Statistics

- Quantititative variables: Student's t-test or Wilcoxon test
- Qualitative variables were expressed as number and percentage and compared using Chi-squared or Fisher's exact test, as appropriate.
- Survival analysis/Kaplan-Meier curve/log-rank test
- Multivariate cox model
- The best multivariate model selected using a descendant stepwise method including only significant variables
- $p<0.05$ value considered statistically significant
- R software version 3.1.3.

RESULTS

Study population



RESULTS

Study population characteristics

	Entire population n= 812 (%)	CV<40 n=578 (%)	CV≥40 n=234 (%)	*p*-value
Gender				
Male	622 (76.6%)	455 (78.7%)	167 (71.4%)	0.03
Female	190 (23.4%)	123 (21.3%)	67 (28.6%)	
Age	56 [15 ; 73]	56 [15 ; 72]	56 [16 ; 73]	0.86
Medical history				
Diabetes mellitus	153 (18.8%)	114 (19.7%)	39 (16.7%)	0.36
Arterial hypertension	86 (10.6%)	68 (11.8%)	18 (7.7%)	0.11
TIPS	35 (4.3%)	26 (4.5%)	9 (3.8%)	0.82
Hepato-renal syndrome	37 (4.6%)	25 (4.3%)	12 (5.1%)	0.76
BMI	26.4 [15.7 ; 47.2]	26.5 [15.7 ; 45.7]	26.0 [17.4 ; 47.2]	0.29
Diagnosis				0.31
HCC	221 (27.2%)	165 (28.5%)	56 (23.9%)	
Alcohol	358 (44.1%)	250 (43.3%)	108 (46.2%)	
Acute liver failure	34 (4.2%)	19 (3.3%)	15 (6.4%)	
Biliary and immunologic	62 (7.6%)	44 (7.6%)	18 (7.7%)	
Viral hepatitis (B+C)	66 (8.1%)	47 (8.1%)	19 (8.1%)	
Other	71 (8.7%)	53 (9.2%)	18 (7.7%)	
HCV infection	79 (9.7%)	52 (9%)	27 (11.5%)	0.33
Child Pugh class				<0.001
A	266 (32.7%)	216 (37.4%)	50 (21.4%)	
B	217 (26.7%)	151 (26.1%)	66 (28.2%)	
C	331 (40.7%)	211 (36.5%)	118 (50.4%)	
MELD score (median value)	14.5 [5.41 ; 40]	13.2 [5.4 ; 40]	17.8 [5.4 ; 40]	<0.001
CKD-EPI value (preoperative)	95.9 [7.5 ; 170.5]	95.9 [11.5 ; 146.4]	96.6 [7.5 ; 170.5]	0.66
Dialysis (preoperative)	13 (1.6%)	7 (1.2%)	6 (2.6%)	0.21
Cold ischemia time (min)	564.5 [183 ; 1148]	568.5 [183 ; 1148]	556.5 [19 ; 930]	0.34
Surgical duration (min)	360 [134 ; 800]	360 [134 ; 743]	370 [175 ; 800]	0.44
Bilioenteric anastomosis	46 (5.7%)	34 (5.9%)	12 (5.1%)	0.80
Donor Gender				0.29
Male	477 (58.6%)	346 (59.9%)	130 (55.6%)	
Female	337 (41.4%)	232 (40.1%)	104 (44.4%)	
Donor age (median value)	53 [10 ; 90]	53.5 [11 ; 87]	53 [10 ; 90]	0.73
Donor BMI (median value)	24.49 [14.02 ; 54.4]	24.49 [14.02 ; 54.4]	24.69 [14.27 ; 48.89]	0.49
ECD graft	451 (55.5%)	322 (55.7%)	127 (54.3%)	0.75

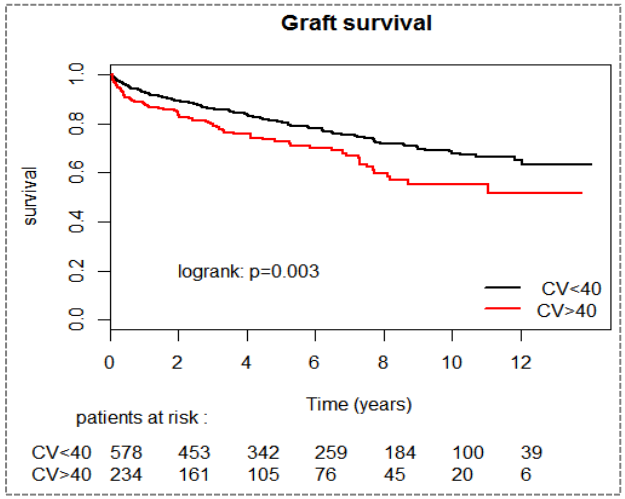
BMI: Body mass index; CKD-EPI: Chronic Kidney Disease - Epidemiology Collaboration; CV: Coefficient of variation; ECD: Extended criteria donor; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; TIPS: Transjugular intrahepatic portosystemic shunts

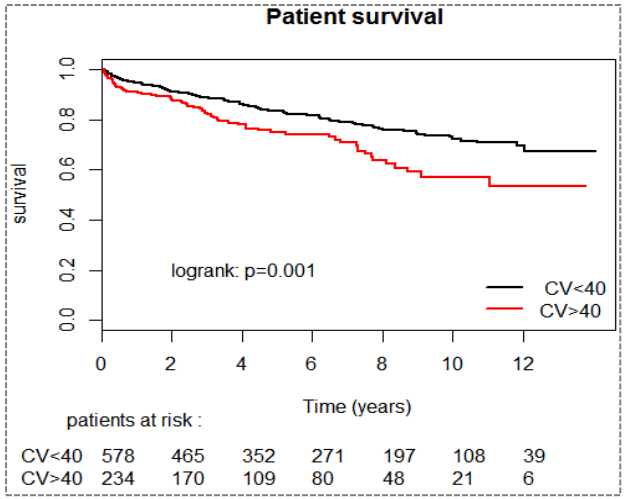
Postoperative outcomes

	Entire population n= 812 (%)	CV<40 n=578 (%)	CV≥40 n=234 (%)	*p*-value
Cardio-vascular complications	104 (15.1%)	56 (9.7%)	46 (19.7%)	0.001
Neurologic complications	171 (24.1%)	96 (16.6%)	73 (31.2%)	<0.001
Dialysis	33 (4.8%)	13 (2.2%)	20 (8.5%)	<0.001
CKD-EPI value (at POD30)	74.8 [7.3 ; 184.3]	75.6 [14.0 ; 151.3]	71.4 [7.3 ; 184.3]	0.34
Acute rejection	144 (17.7%)	98 (17%)	46 (19.7%)	0.42
EAD incidence	157 (19.5%)	104 (18%)	52 (22.2%)	0.21
Arterial complications	17 (2.2%)	11 (1.9%)	6 (2.6%)	0.83
Biliary complications	58 (7.1%)	37 (6.4%)	21 (9%)	0.26
ICU stay	4 [1; 199]	4 [1; 199]	5 [1; 148]	<0.001
Hospitalization duration	19 [2; 333]	18 [2; 333]	23 [3; 232]	<0.001
TAC trough concentration (ng/mL) (mean value within first POD 30)	9.8 ±6.3	10.0 ±5.9	9.3 ±5.9	0.009
Mean number of dosages (within first POD 30)	14 [4 ; 29]	14 [5 ; 29]	15 [4 ; 29]	0.10
Outcomes				
3-month graft survival	787 (96.7%)	563 (97.4%)	222 (94.9%)	0.108
1-year graft survival	744 (91.4%)	536 (92.7%)	206 (88%)	0.043
3-month patient survival	796 (97.8%)	568 (98.3%)	226 (96.6%)	0.224
1-year patient survival	762 (93.6%)	547 (94.6%)	213 (91%)	0.081

CKD-EPI: Chronic Kidney Disease - Epidemiology Collaboration; CV: Coefficient of variation; EAD: early allograft dysfunction; ICU: intensive care unit; POD: Post-operative day; TAC: tacrolimus

RESULTS





Univariate and multivariate analysis of graft survival

Variables	Univariate (Logrank Test) p	Multivariate (Cox Model) p	Hazard Ratio	[CI 95%]
Recipient gender	0.09	ns		
Age (years)	0.64	-		
BMI*	0.78	-		
HCV infection	0.02	0.04	1.49	[1.01; 2.19]
Liver malignancy	0.03	0.03	1.36	[1.03; 1.79]
Child-Pugh grade	0.63	ns		
MELD score	0.71	ns		
Donor age	0.70	-		
ECD graft	0.11	ns		
EAD	0.38	ns		
CV≥40	0.003	0.002	1.57	[1.18; 2.01]
Mean TAC concentration	0.6	-		

BMI: Body mass index; CV: Coefficient of variation; ECD: Extended criteria donor; EAD: early allograft dysfunction; TAC: tacrolimus

DISCUSSION

TAC C0 CV in the early period post transplantation ≠ other studies focused beyong 6 months

- Unstable patients, CV reflects several sources of variability within the first month
- First data in OLT about long term consequences of IPV in the early period post transplantation
- After 6 months: reflect mainly the patient nonadherence

A high TAC C0 CV is associated with more neurotoxicity, cardiotoxicity, acute renal failure requiring dialysis

- Mean TAC C0 significantly lower in the high-CV group but still remained within the normal therapeutic range
- → TAC C0 uncomplete biomarkers to manage TAC treatment
- Alternation of overexposure and underexposure to TAC → results in organ toxicity more than constant exposure?
- Causality relationship remains to be clearly established

A high TAC C0 CV is a risk factor for poorer long-term graft survival and patient's survival

- high CV → sub-acute rejection with infraclinic liver parenchyma lesion → clinically relevant in the long-term

Risk of presenting a high-CV : pre-transplantation liver dysfunction severity (elevated MELD score and Child-Pugh grade)

- Patient with longer graft function restauration (altered liver environment) → pharmacokinetics parameters instability

Limits of the study:

- Retrospective, Monocentric, observational → to be confirmed in a prospective study
- Many factors of variability in the early period (but strict selection criteria to decrease bias)

CONCLUSION

Risk factors for presenting a high CV:
A pre-transplantation elevated MELD score and Child-Pugh grade

High intra-patient variability of TAC C0 within the first month post LT (adults)

- Association with TAC safety (complications)
- Impact on TAC efficacy (patients and graft outcomes)

How to prevent IPV in the early period post LT?

Assess risk-patients to intensive therapeutic education program

Choice of the first dose:

- Pharmacogenetics (CYP3A5)
- Lower first dose

To refine TDM :

- TAC monitoring in new matrice: intra-PBMC, biliary TAC
- Area under the curve (microsampling ++)
- Computer algorithms to adjust dosage

↑ Personalisation of TAC therapy

THANK YOU FOR YOUR ATTENTION

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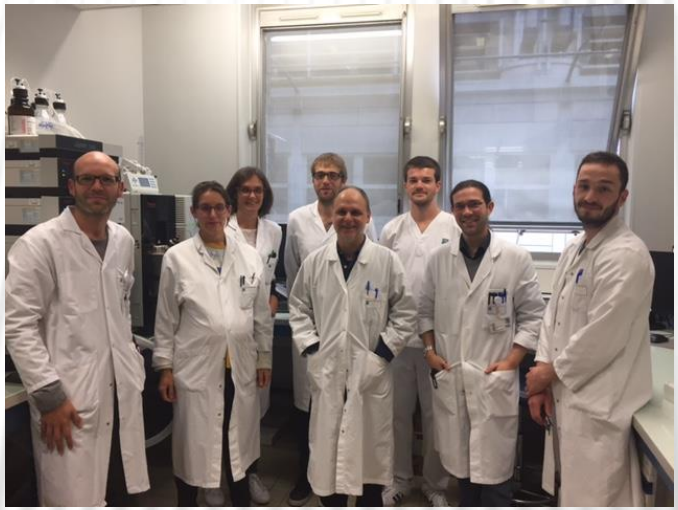

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