Généralités sur le suivi thérapeutique pharmacologique (STP)

2023-2024

1) STP ?

1) STP immunosuppresseurs (tacrolimus, MPA)

2) STP du voriconazole

3) STP Anticorps monoclonaux

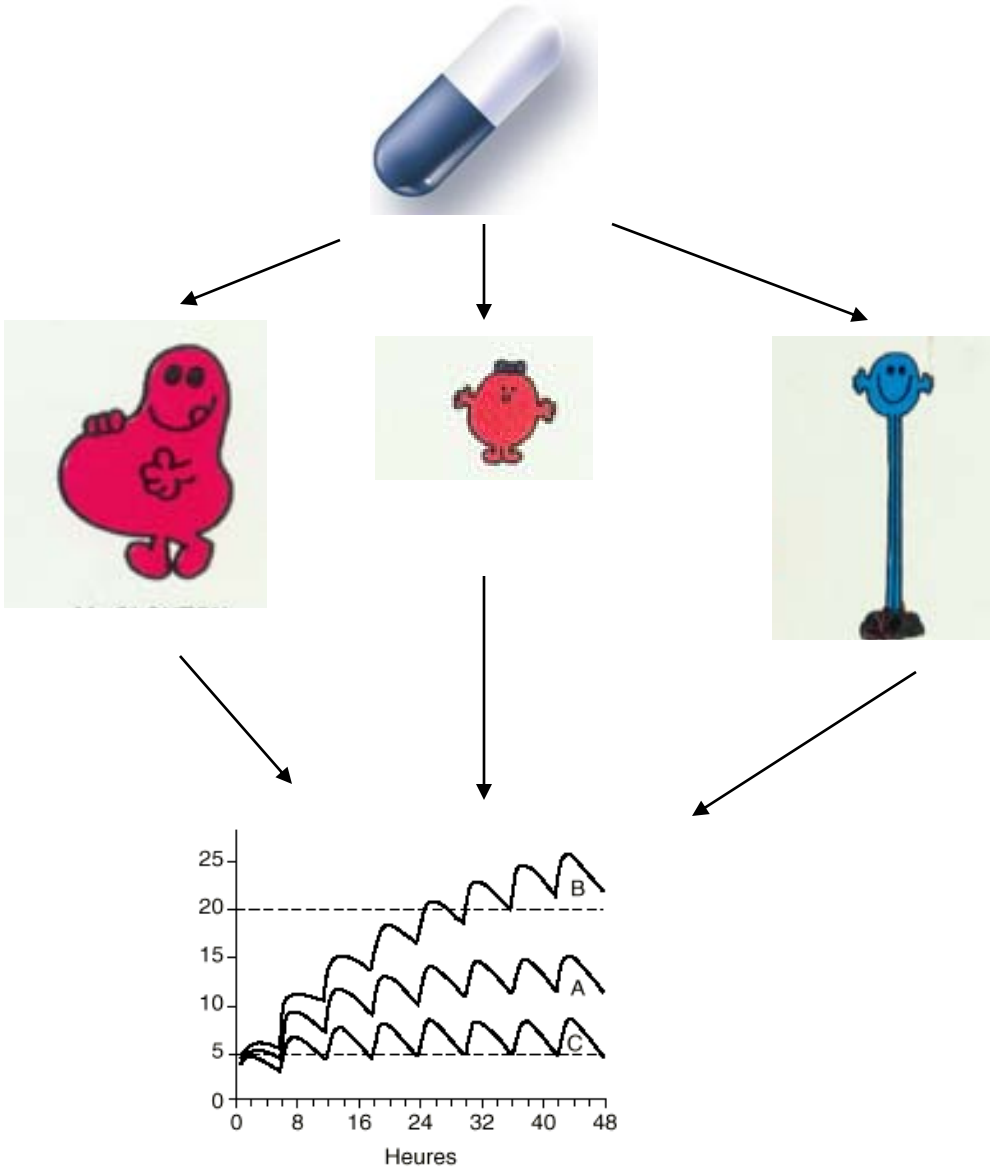
1) STP ?

1-1 Définition

Suivi Thérapeutique Pharmacologique (STP)

= Therapeutic Drug Monitoring (TDM)

« Adaptation individuelle de la prescription basée sur la mesure d'un paramètre d'exposition à un médicament »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Heures
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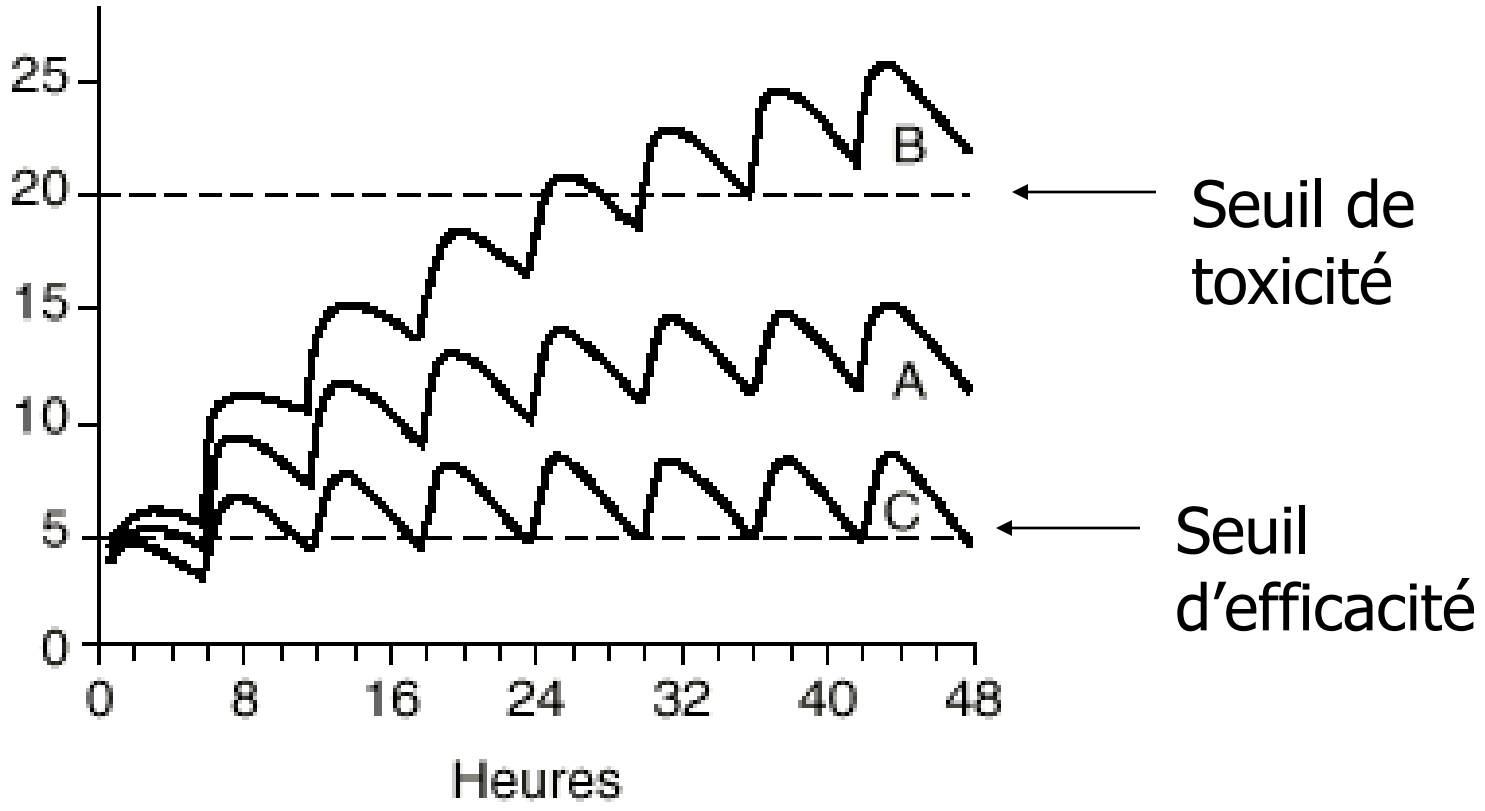
A
C


25
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16
24
32
40
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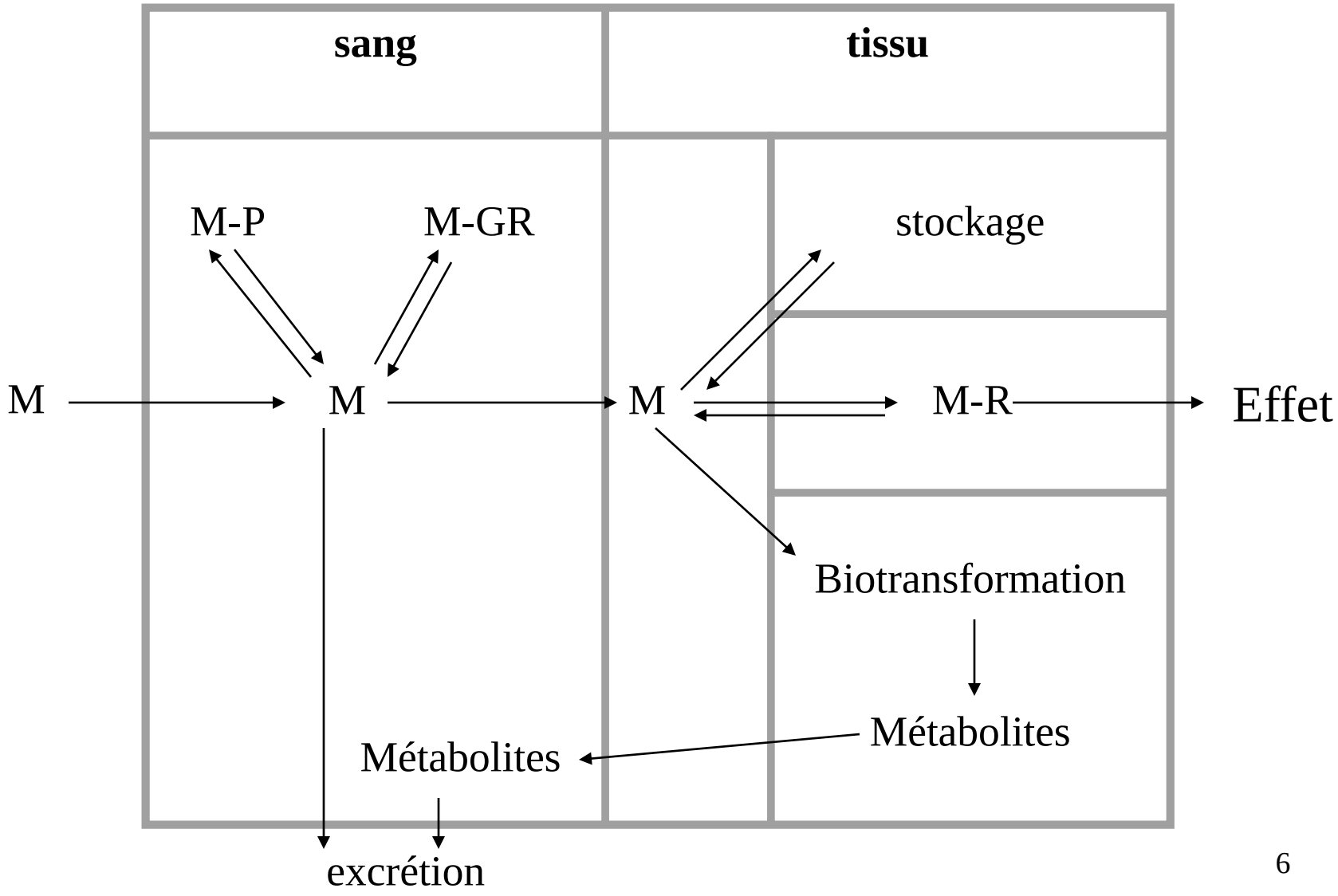
Heures
B
A
C
Seuil de toxicité
Seuil d'efficacité

Pourquoi mesurer la concentration sanguine/plasmatique? :

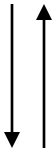
Concentration sanguine/plasmatique $\rightleftharpoons$ Concentration au site d'action



1-2 Conditions pour faire du STP

- *Existence de la relation*:

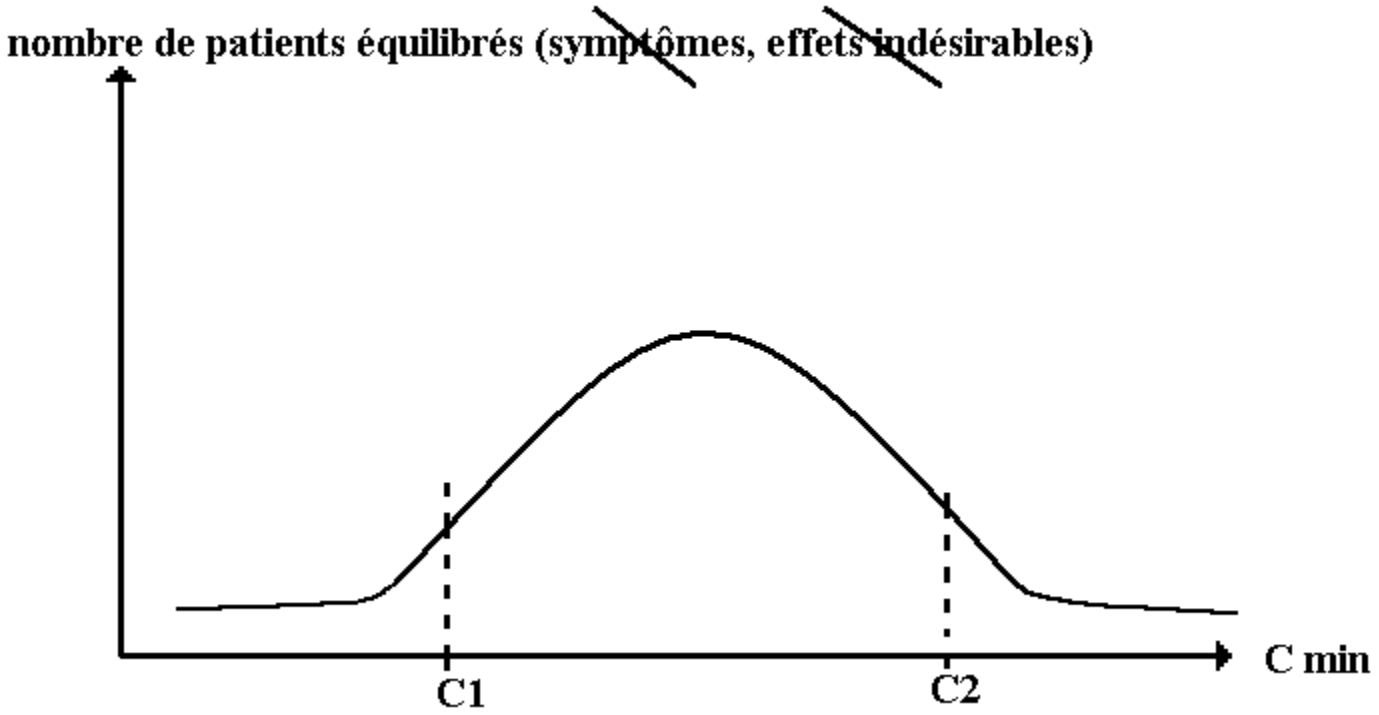
Concentration sanguine/plasmatique



Concentration au site d'action

Effet pharmacodynamique (thérapeutique ou toxique)

- *Zone thérapeutique*



⇒ Indice prédictif d'activité ≠ critère d'efficacité

- *Technique analytique: sensible, spécifique*

⇒ immunologique, chromatographique (LCMSMS)…

- *Essais cliniques prospectifs:*

Groupe de patients avec STP : « concentration contrôlée »

↑ ou ↓ posologie en fonction des résultats du paramètre d'exposition par rapport à la zone thérapeutique

Groupe de patients sans STP : problème éthique

⇒ ↓ échec thérapeutique avec STP ?

⇒ niveau de preuve +++ pour le STP

Indications du STP

- *médicaments à faible marge thérapeutique*

- *pas de marqueur de l'activité pharmacodynamique (glycémie) ou réponse à distance (rejet de greffon)*

Ex : immunosuppresseurs

- *variabilité inter et/ou intra- individuelle de la pharmacocinétique d'un médicament*

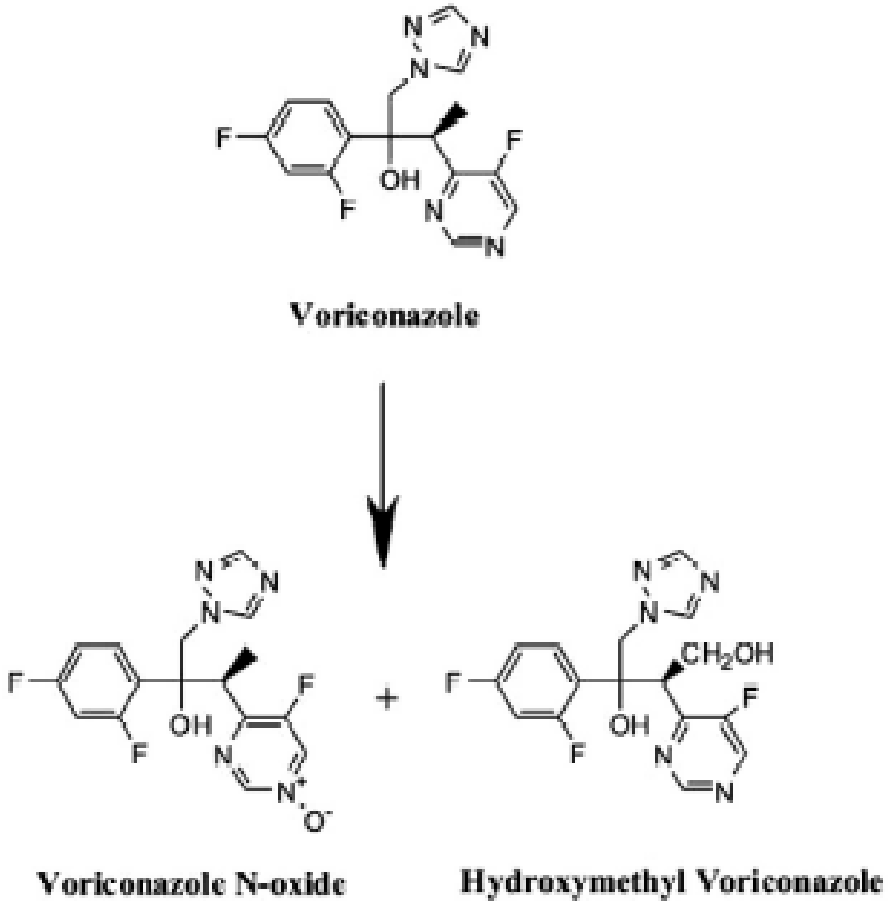
- *(mauvaise observance)*

Causes de la variabilité inter et/ou intra-individuelle de la pharmacocinétique

- Facteurs physiopathologiques :
  I rénale, I hépatique…

- Interactions médicamenteuses :
  inhibiteurs, inducteurs enzymatiques…

- Polymorphisme génétique des enzymes métaboliques (CYP 2D6, 2C9, 2C19…) + épigénétique

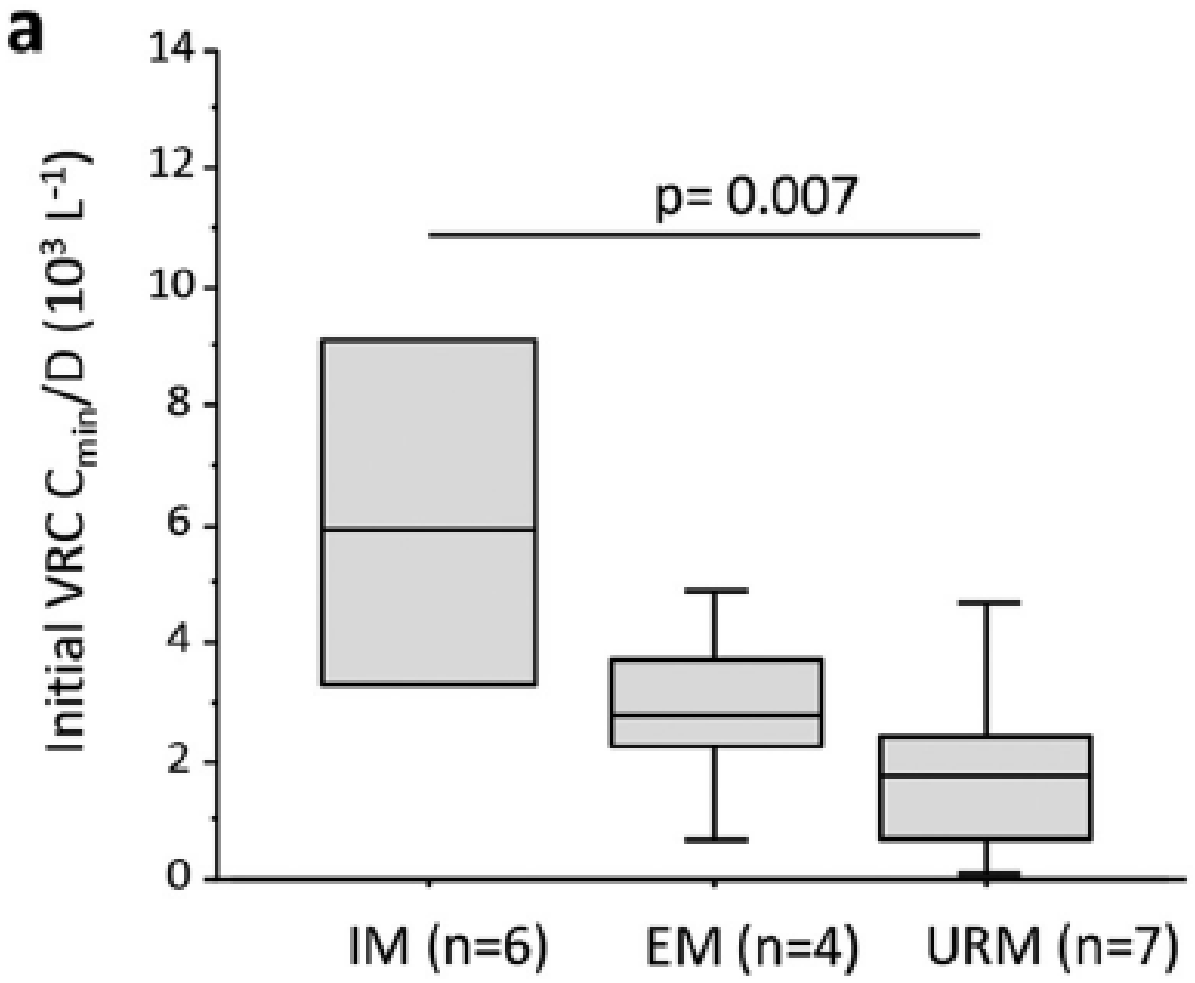


- Polymorphisme génétique (CYP 450 2C19, 3A4, 3A5)

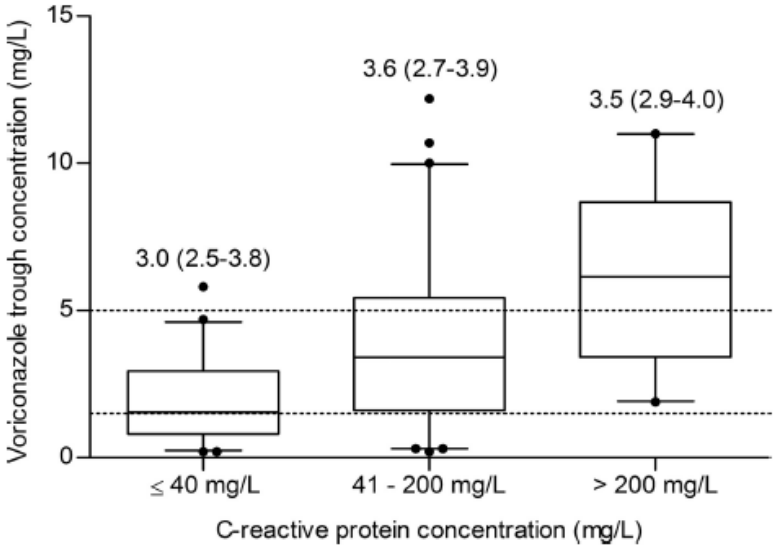
Yanni et al Drug metabolism disposition, 2010

polymorphisme génétique (SNIP)

Voriconazole et phénotypage CYP 450 2C19



Gautier-Veyret E et al AAC 2015



van Wanrooy, 2014, AAC

1521-009X/43/3/400–410$25.00
DRUG METABOLISM AND DISPOSITION

http://dx.doi.org/10.1124/dmd.114.061093
Drug Metab Dispos 43:400–410, March 2015

Minireview

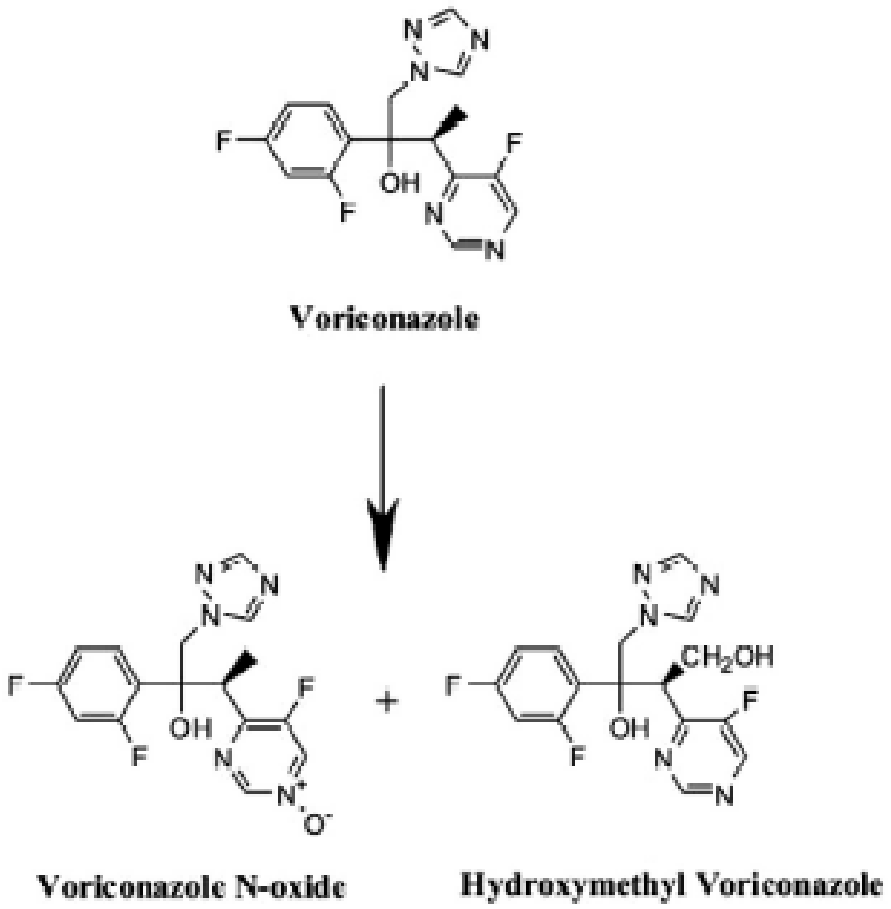
Inflammation-Induced Phenoconversion of Polymorphic Drug Metabolizing Enzymes: Hypothesis with Implications for Personalized Medicine

Rashmi R. Shah and Robert L. Smith

Rashmi Shah Consultancy Ltd., 8 Birchdale, Gerrards Cross, Buckinghamshire, United Kingdom (R.R.S.); and Department of Surgery and Cancer, Faculty of Medicine, Imperial College, South Kensington campus, London, United Kingdom (R.L.S.)

Received September 10, 2014; accepted December 17, 2014

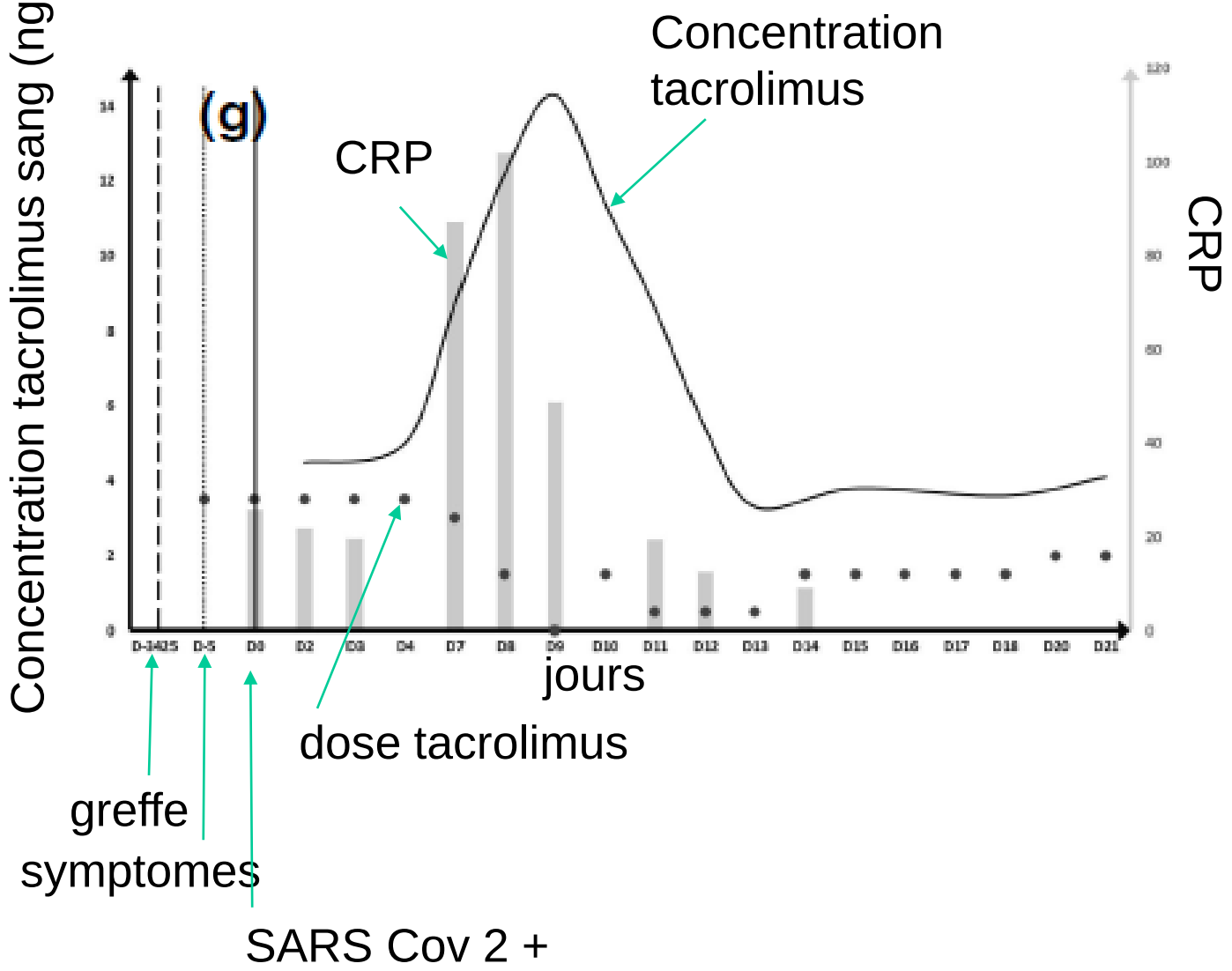
Inflammation⇒ cytokines : EM → PM ?
phénotypage > génotypage



- Polymorphisme génétique (CYP 450 2C19, 3A4, 3A5)
- Facteurs environnementaux (inflammation)

Yanni et al Drug metabolism disposition, 2010

SARS Cov2 et STP tacrolimus



Clin Pharmacol Ther , 2022

niveau de preuve

Etude prospective randomisée :
STP vs contrôle

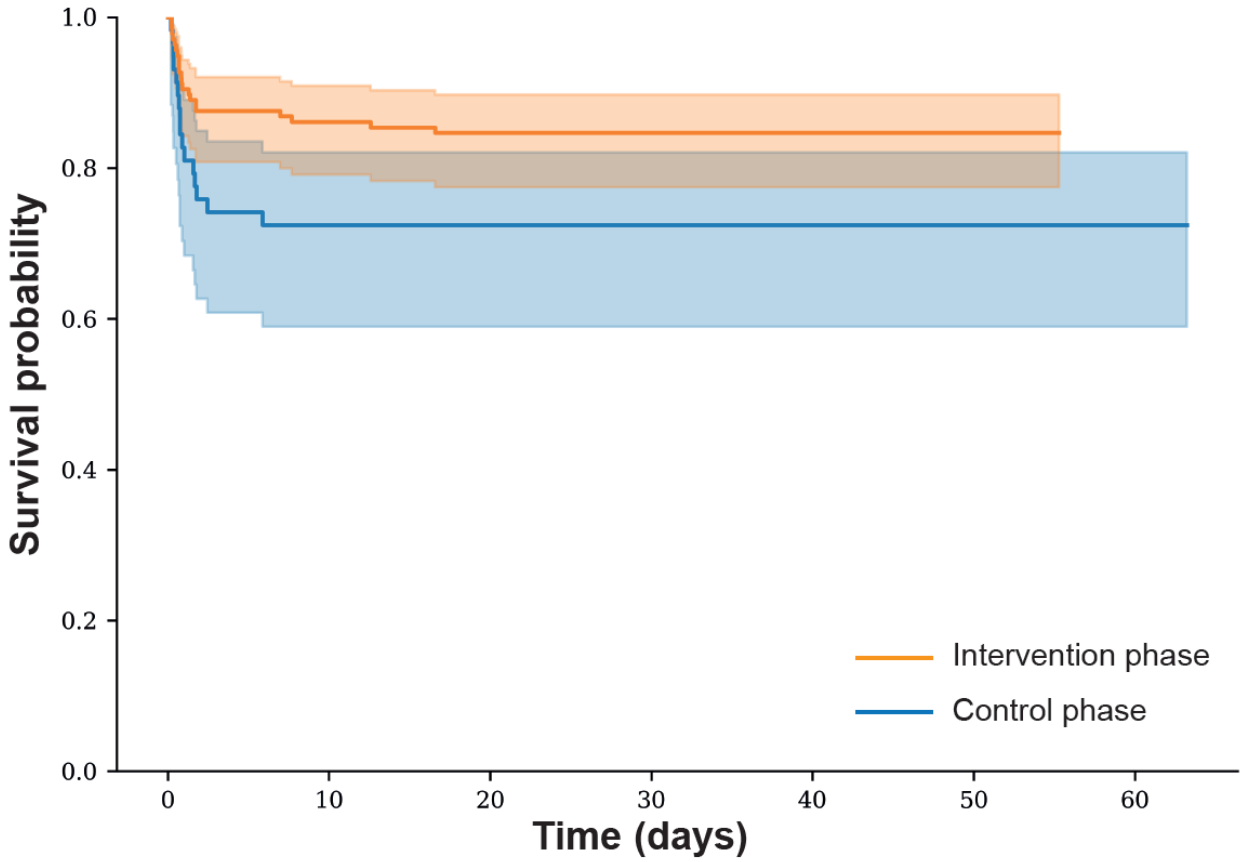
Etude avant/après: soins standards/soins avec STP

Etude relation PK –PD prospective

Etude relation PK –PD rétrospective

Cas clinique

A multifaceted strategy to optimize pharmacokinetics of antimicrobial therapy in patients with hospital-acquired infections - a monocenter quality improvement project



Lagarde C et al JAC 2023

American Journal of Transplantation
Volume 7, Issue 11, November 2007, Pages 2496-2503

Individualized Mycophenolate Mofetil Dosing Based on Drug Exposure Significantly Improves Patient Outcomes After Renal Transplantation

Y. Le Meur [a], M. Büchler [b], A. Thierry [c], S. Caillard [d], F. Villemain [e], S. Lavaud [f], I. Etienne [g], P.-F. Westeel [h], B.H. De Ligny [i], L. Rostaing [j], E. Thervet [k], J.C. Szelag [a], J.-P. Rérolle [a], A. Rousseau [l], G. Touchard [c], P. Marquet [m]

Efficacy and safety of mycophenolate mofetil (MMF) may be optimized with individualized doses based on therapeutic monitoring of its active metabolite, mycophenolic acid (MPA). In this 12-month study, 137 renal allograft recipients from 11 French centers receiving basiliximab, cyclosporine A, MMF and corticosteroids were randomized to receive either concentration-controlled doses or fixed-dose MMF. A novel Bayesian estimator of MPA AUC based on three-point sampling was used to individualize doses on posttransplant days 7 and 14 and months 1, 3 and 6. The primary endpoint was treatment failure (death, graft loss, acute rejection and MMF discontinuation). Data from 65 patients/group were analyzed. At month 12, the concentration-controlled group had fewer treatment failures ($p = 0.03$) and acute rejection episodes ($p = 0.01$) with no differences in adverse event frequency. The MMF dose was higher in the concentration-controlled group at day 14 ($p < 0.0001$), month 1 ($p < 0.0001$) and month 3 ($p < 0.01$), as were median AUCs on day 14 (33.7 vs. 27.1 mg•h/L; $p = 0.0001$) and at month 1 (45.0 vs. 30.9 mg•h/L; $p < 0.0001$). Therapeutic MPA monitoring using a limited sampling strategy can reduce the risk of treatment failure and acute rejection in renal allograft recipients 12 months posttransplant with no increase in adverse events.

2) STP immunosuppresseurs

Immunosuppresseur : ciclosporine /tacrolimus + MPA + corticoïdes

2-1) tacrolimus

Transplantation rénale

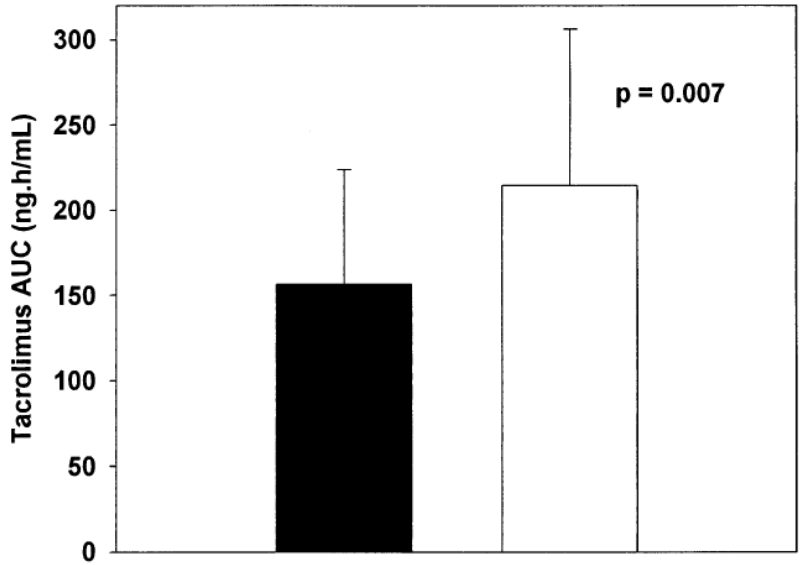


Fig 2. Mean (±SD) FK 506 AUC_{0-12} on day 2 in patients who had experienced at least one rejection episode and in patients who remained rejection free. ■, patients experiencing a rejection episode (n = 17); □, patients remaining rejection free (n = 39).

Undre Na et al, Transplant Proc. 1999

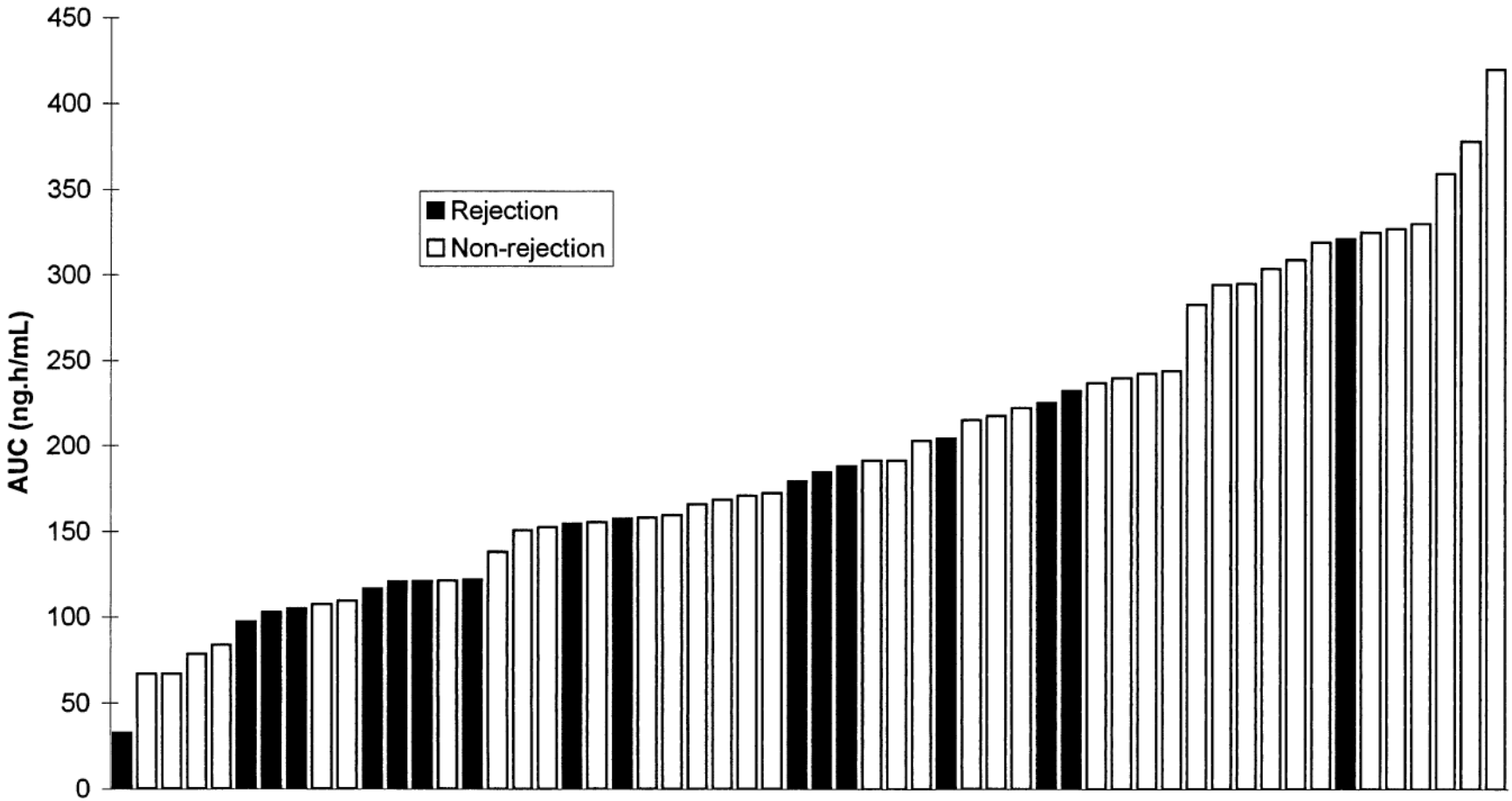


Fig 1. Individual AUC_{0-12} on day 2 in patients with and without rejection.

Undre Na et al, Transplant Proc. 1999 [21]

figure 1 -1 (TAC)

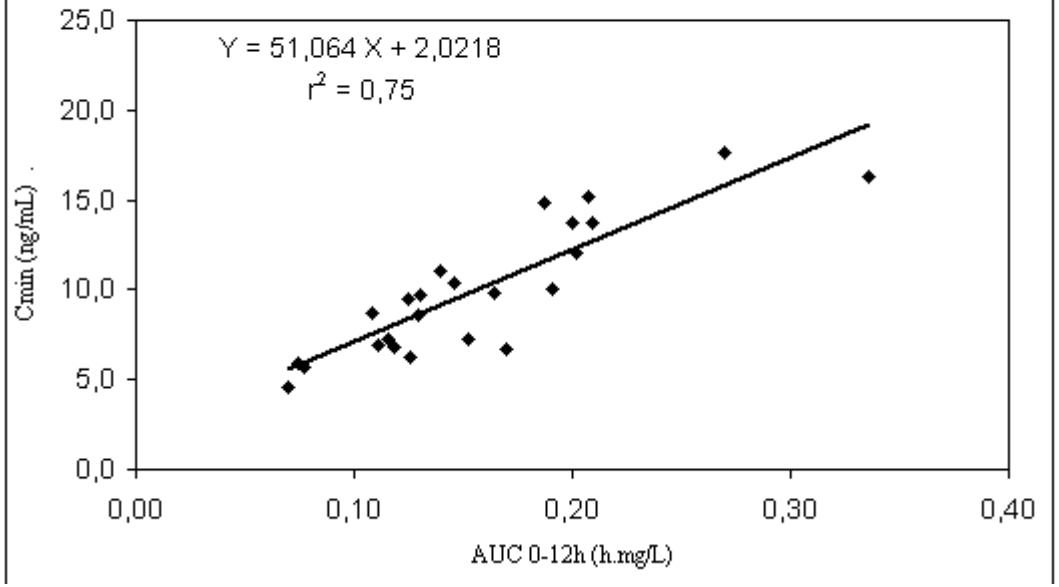
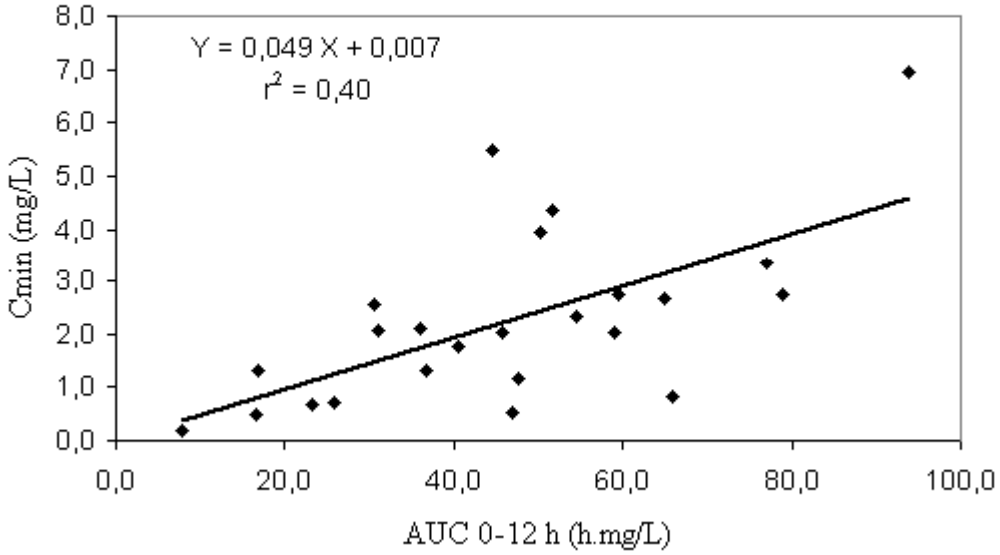


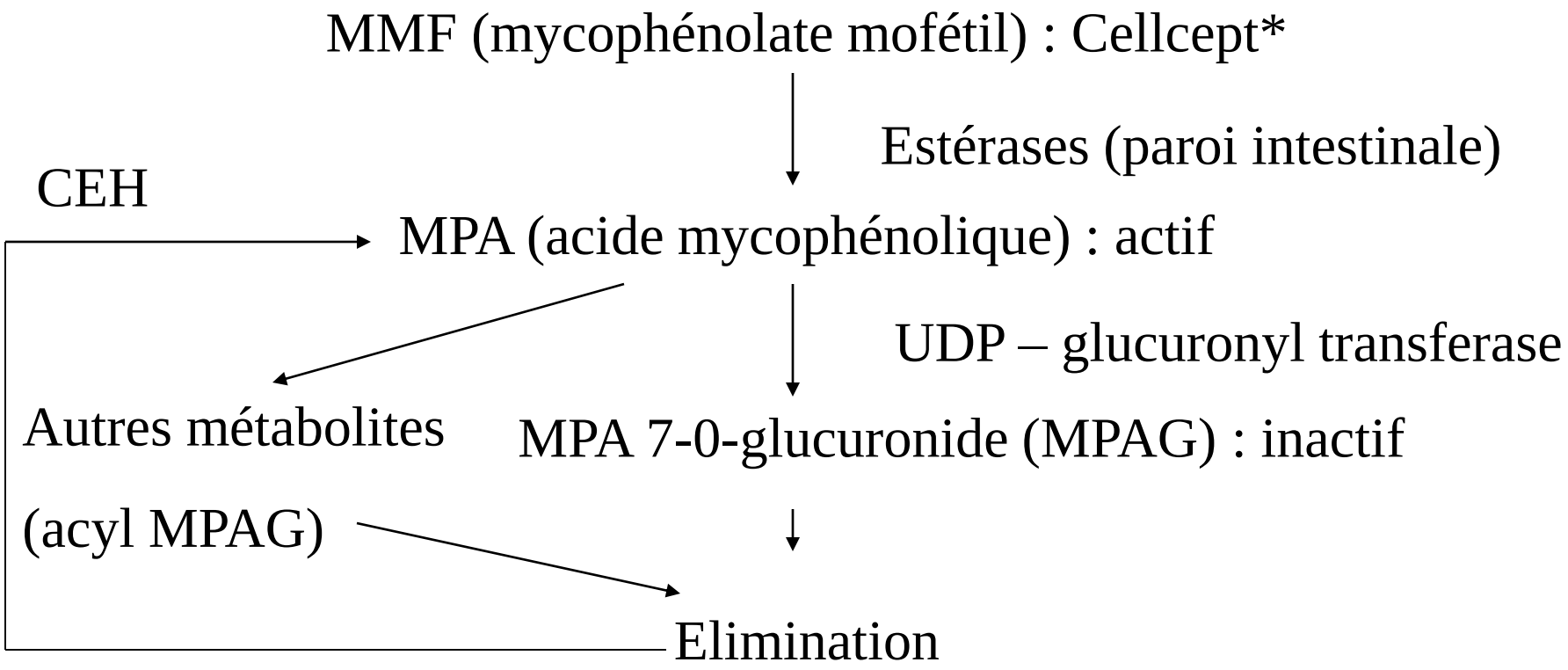
figure 1-2 (MPA)



Rein-pancreas

2-2) STP de l'acide mycophénolique

Immunosuppresseur : CsA/Tacro + MPA + corticoïdes



Cycle Entéro Hépatique

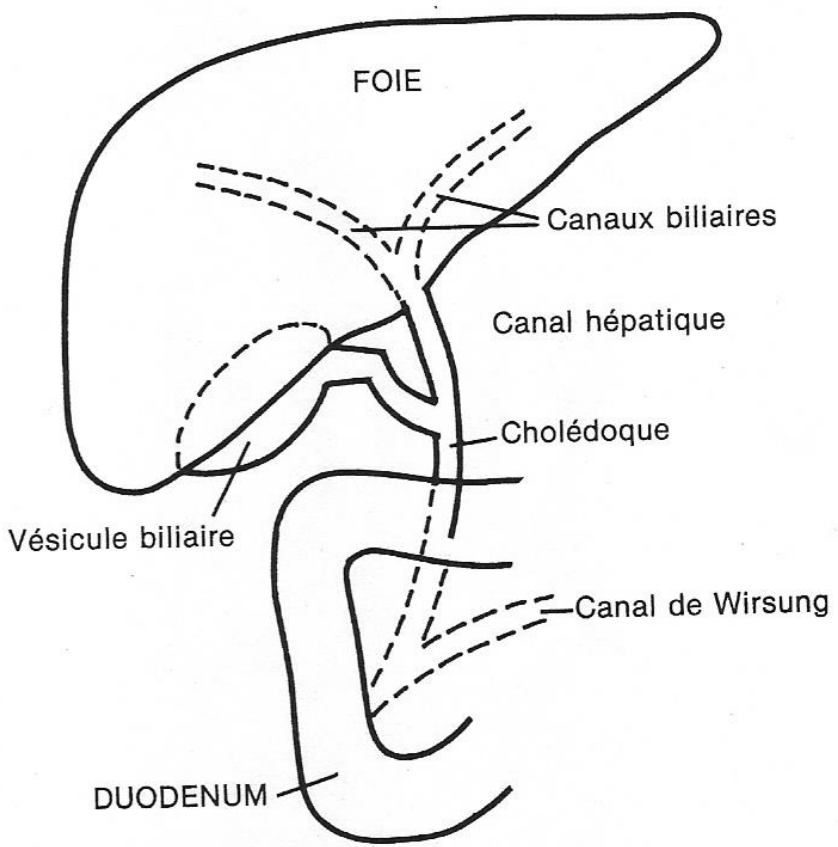
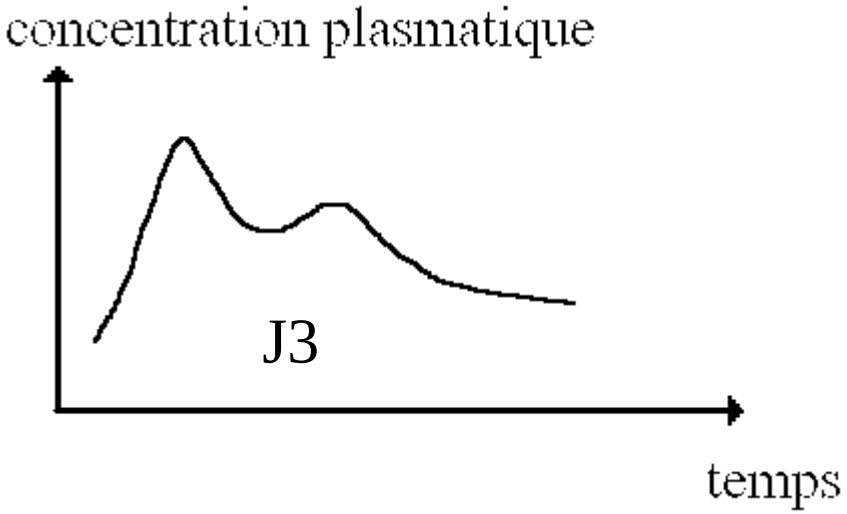
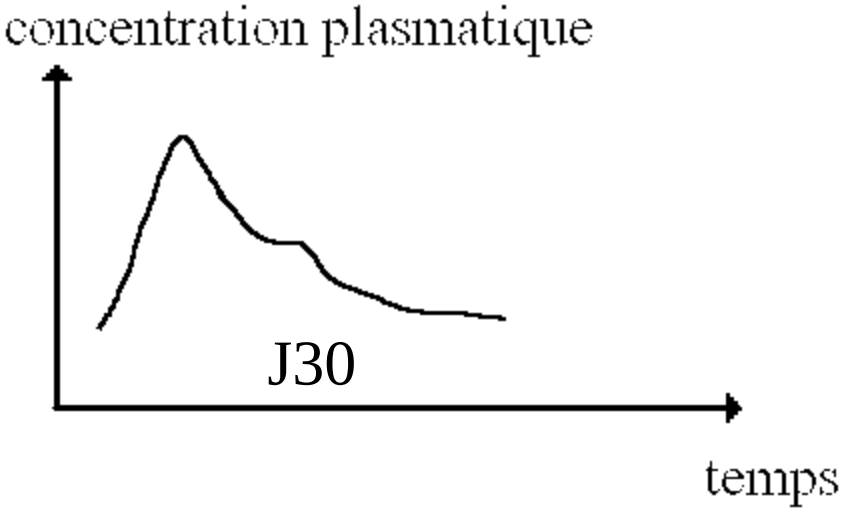
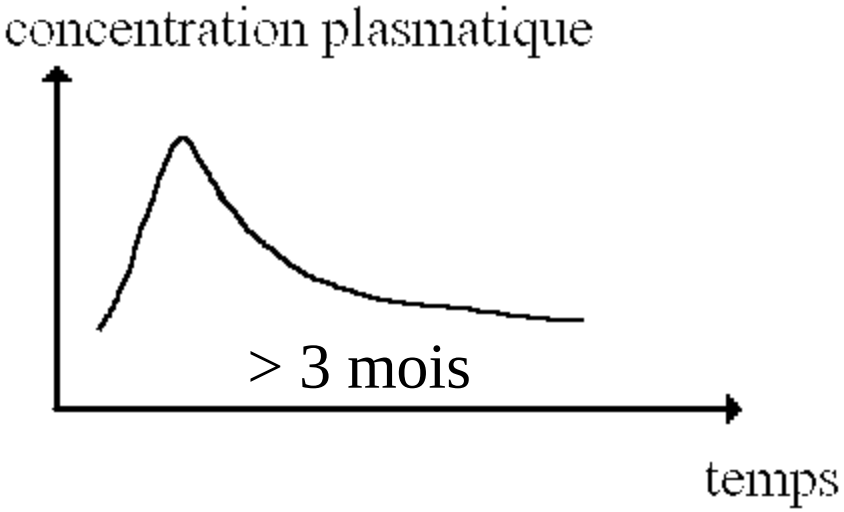


Figure 9 : Schéma du système biliaire : le médicament excrété par les hépatocytes dans les canalicules biliaires, est déversé par le choledoque dans le duodénum d'où il peut être réabsorbé (cycle entérohépatique).

Variabilité intra individuelle : MPA







-traitements associés (CsA, corticoïdes)

-Fonction du greffon

-Liaison protéique…

Variabilité inter-individuelle : MPA

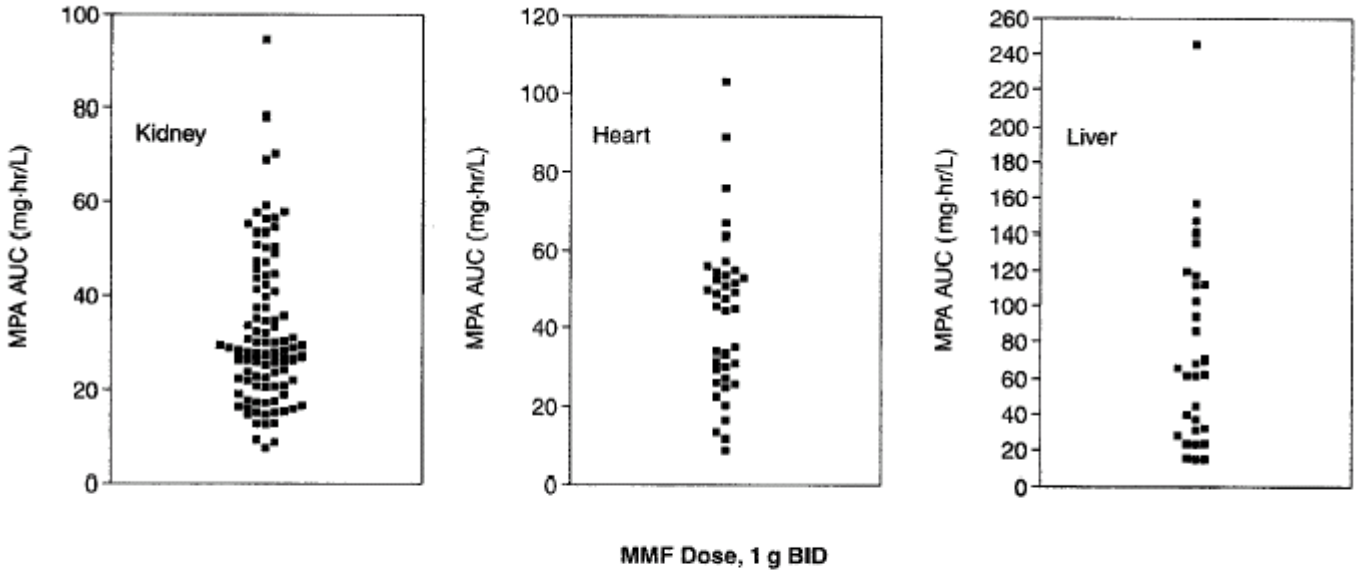


Figure 1: Mycophenolic acid (MPA) AUC values for cohorts of renal, heart and liver transplant patients. These data are adapted from (15,19,20), respectively. All MPA AUC values have been dose-normalized to 1 g mycophenolate mofetil (MMF) bid.

16.1 µg x h /ml

32.2 µg x h /ml

60.6 µg x h /ml

	Target MPA AUC		
	Low	Intermediate	High
Number of patients	51	47	52
Biopsy-proven rejection	14/51 (27.5%)	7/47 (14.9%)	6/52 (11.5%)
Presumed rejection	3	2	3
Treated for rejection with negative biopsy	0	2	1
Corticosteroid treatment	12/51 (23.5%)	6/47 (12.8%)	6/52 (11.5%)
OKT3/ATG treatment	7/51 (13.7%)	3/47 (6.4%)	2/52 (3.9%)

Table 4. Incidence and treatment of acute rejection in the three target MPA AUC groups within the first 6 months after transplantation (on-study and post-termination)

$\Rightarrow$ AUC0-12H = 30–60 µg x h /ml

van Gelder T. et al.Transplantation: Volume 68(2) 27 July 1999 pp 261-266

Table 3: Receiver operating characteristic (ROC) curve analysis: Area under ROC curve (95% confidence interval, CI and probability, p) in prediction of rejection and toxicity

	Rejection			Toxicity		
Day 3	Area	95% CI	p	Area	95% CI	p
MPA C0	0.65	0.48–0.81	0.08	0.49	0.37–0.62	0.90
MPA C2	0.68	0.55–0.82	0.025	0.52	0.39–0.65	0.77
MPA AUC0-12	0.72	0.60–0.88	0.007	0.53	0.40–0.66	0.29
C2 (CyA)	0.63	0.49–0.81	0.11	0.46	0.33–0.58	0.98

MPA = mycophenolic acid.

⇒MPA : AUC 0-12 > C0

⇒AUC : méthode Bayésienne (T20 min, T1H, T3H)

Kiberd BA. Et al, Am J Transplant. 2004 Jul;4(7):1079-83.

- Apomygre

Greffe rénale

MMF : dose fixe versus dose ajusté en f(AUC)

↓ Risque rejet à un an après la greffe dans le bras avec adaptation de la dose en f(AUC)

3) Voriconazole (V-fend®)

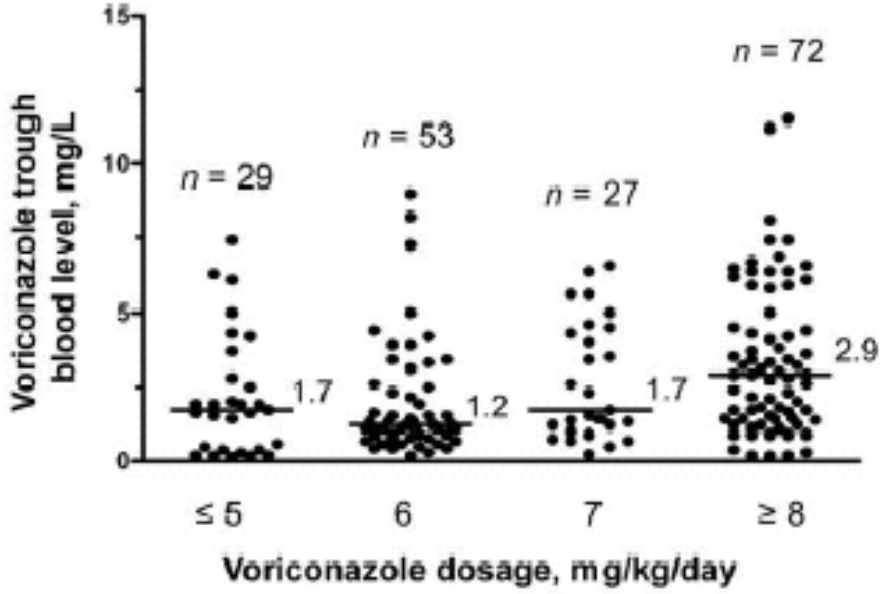


Figure 1. Relationship between voriconazole dosage and voriconazole trough blood level. Each point represents a single blood level measurement. Numbers of measurements for each daily dose are reported. Horizontal bars represent median values (the numerical values are reported on the right of the horizontal bar for each group). Voriconazole dosages have been rounded to the nearest unit.

Pascual et al Clin Infect Dis. 2008

voies métaboliques : substrat/ inhibiteur

rifabutine+voriconazole *(Schwieson et al Pharmacotherapy 2008)*

	CYP 3A4	CYP 2C9	CYP 2C19	CYP 2D6	CYP 2E1	CYP 1A2	UGT	Pgp
Itraconazole	+/+							+/+
Voriconazole	+/+	+/+	+/+					
Posaconazole	+						+	+

Polymorphisme génétique *(Weiss et al J Clin Pharmacol 2009)*

Nivoix et al Clin Pharmacokinet 2008

voriconazole
Relation concentration effet

- prospective
- n = 52 IFI
- Adaptation de posologie en fonction Cmin
- ↑ ou ↓ posologie

Table 2. Voriconazole trough blood levels and clinical response to antifungal therapy.

Variable	Voriconazole trough blood level: ≤1 mg/L (*n* = 13)	Voriconazole trough blood level: >1 mg/L (*n* = 39)	*P*
Route of voriconazole administration			.05
Intravenous	4 (31)	24 (61)	
Oral	9 (69)	15 (39)	
Voriconazole dosage, median mg/kg/day (range)			
Overall	7 (2.5–9)	8 (2–11)	NS
Intravenous	7.5 (7–8)	8 (6–11)	NS
Oral	6 (2.5–9)	7 (2–11)	NS
Response to antifungal therapy			
Interval between start of voriconazle therapy and assessment, median days (range)	21 (10–120)	17.5 (10–180)	NS
Treatment success			
Overall	7 (54)[a]	34 (88)	.02
Complete response	5	27	
Partial response	2	7	
Lack of response	6 (46)	5 (12)	
Persistence	3 (23)	0 (0)	
Progression	3 (23)	4 (10)	
Breakthrough IFI	0 (0)	1 (2)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. NS, not significant.

[a] In 1 patient, comedication with rifampin resulted in low voriconazole blood levels.

↑ posologie = guérison

Table 4. Voriconazole (Vor) trough blood levels and safety of antifungal therapy.

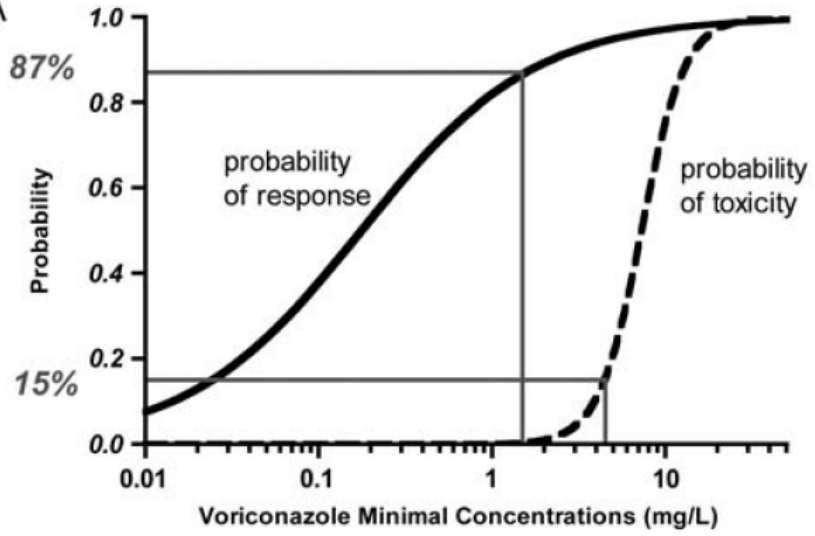
Variable	Vor trough blood level ≤5.5 mg/L (*n* = 36)	Vor trough blood level >5.5 mg/L (*n* = 16)	*P*
Vor route			.07
Intravenous	15 (42)	13 (81)	
Oral	21 (58)	3 (19)	
Vor dosage, median mg/kg/day (range)			
Overall	7 (2–11)	8 (6–11)	.13
Intravenous	7.5 (6–10)	8 (6–11)	NS
Oral	6 (2–11)	7 (6–8)	NS
Serious adverse event			
Encephalopathy			
Incidence	0	5 (31)	.002
Interval after start of Vor, days (range)	NA	9 (5–30)[a]	
Cholestatic hepatopathy			
Incidence	3 (8)	3 (19)	NS
Interval after start of Vor, days (range)	50 (5–150)	13 (6–20)	NS
Concomitant therapy			
Omeprazole	6 (17)	7 (44)	.04
Tacrolimus	0	1 (6)	NS

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] The time interval elapsed between start of Vor therapy and documentation of Vor blood levels >5.5 mg/L in patients without encephalopathy was a median of 5 days (range, 2–7 days); $P = .04$, vs. time interval in patients with encephalopathy.

arrêt ou ↓ posologie

A



B

VRC trough plasma concentration (mg/L)	Probability of response of IFI to VRC therapy	Probability of grade 3 neurotoxicity associated with VRC
0.5	72%	0%
1.0	82%	0%
1.5	**87%**	0.3%
2.0	89%	1%
4.0	93%	11%
4.5	94%	**15%**
5.0	95%	21%
5.5	95%	27%

Figure 2. *A*, Logistic regression model predicting the probability of response to voriconazole (VRC) therapy (solid line) and of grade 3 neurotoxicity probably associated with VRC therapy (dashed line) as a function of the VRC trough plasma concentration. The vertical dotted lines indicate the identified 1.5–4.5 mg/L therapeutic range. *B*, VRC trough plasma concentrations and probabilities predicted by the logistic regression models for (1) response of infection to VRC therapy and (2) grade 3 neurotoxicity associated with VRC. The VRC trough plasma concentration range associated with a >85% probability of response to therapy and a <15% probability of neurotoxicity related to therapy is highlighted in gray and bold.

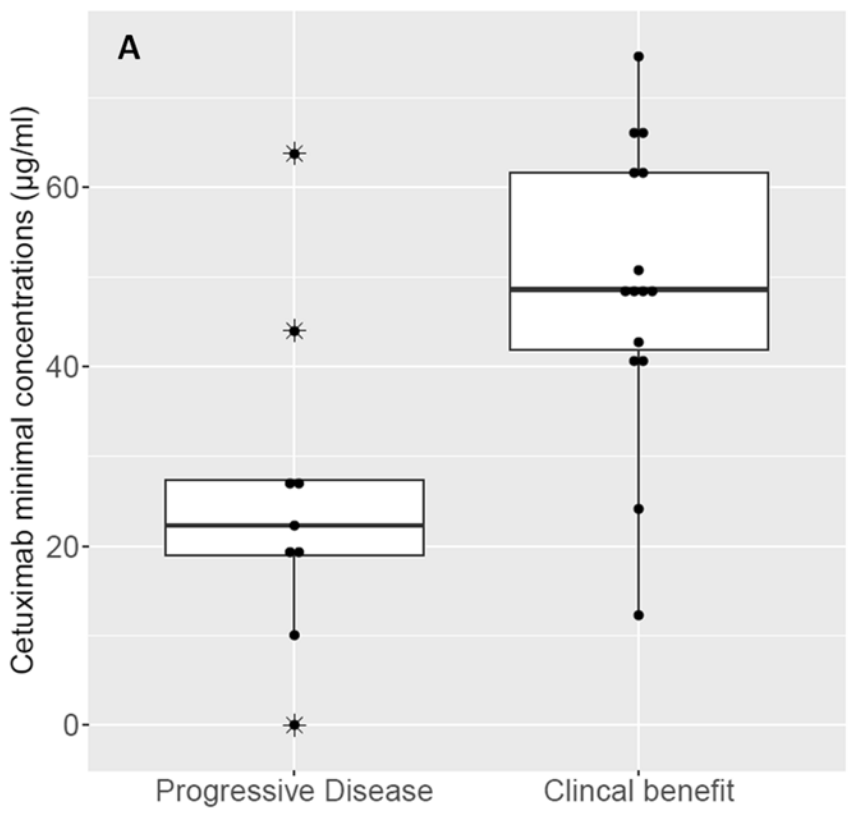
$\Rightarrow$ 1.5 mg/l $\leq$ Cmin $\leq$4.5 mg/l

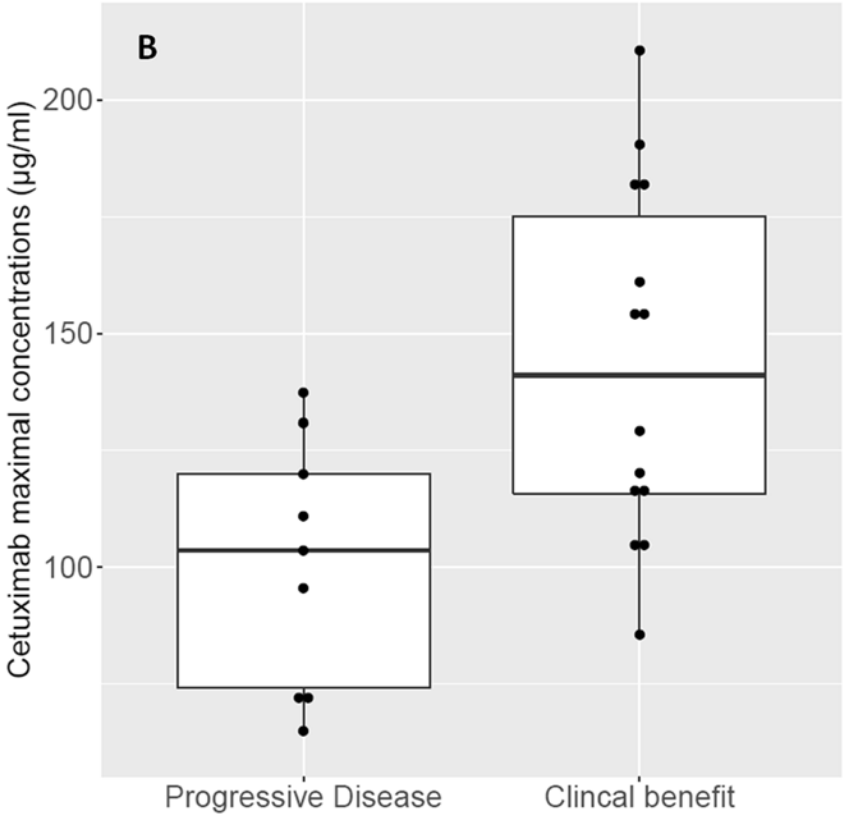
Pascual et al , CID, 2012

3) STP des anticorps monoclonaux

cétuximab

- Anti EGFR (epidermal growth factor receptor)
- cancer colorectal métastatique si pas de mutation (RAS sauvage)
- Ex : carcinome épidermoïde de la tête et du cou





proof of concept
n= 25

Becher et al. Scientific Reports, 2017

Marqueurs d'exposition au traitement

- **Concentration résiduelle:** tacrolimus, voriconazole, cétuximab (?)
- **AUC0-12H** à l'équilibre : MPA