Prophylaxie en TOS et STP

R. GUILLEMAIN (Paris, HEGP)
EM. BILLAUD (Paris, HEGP)

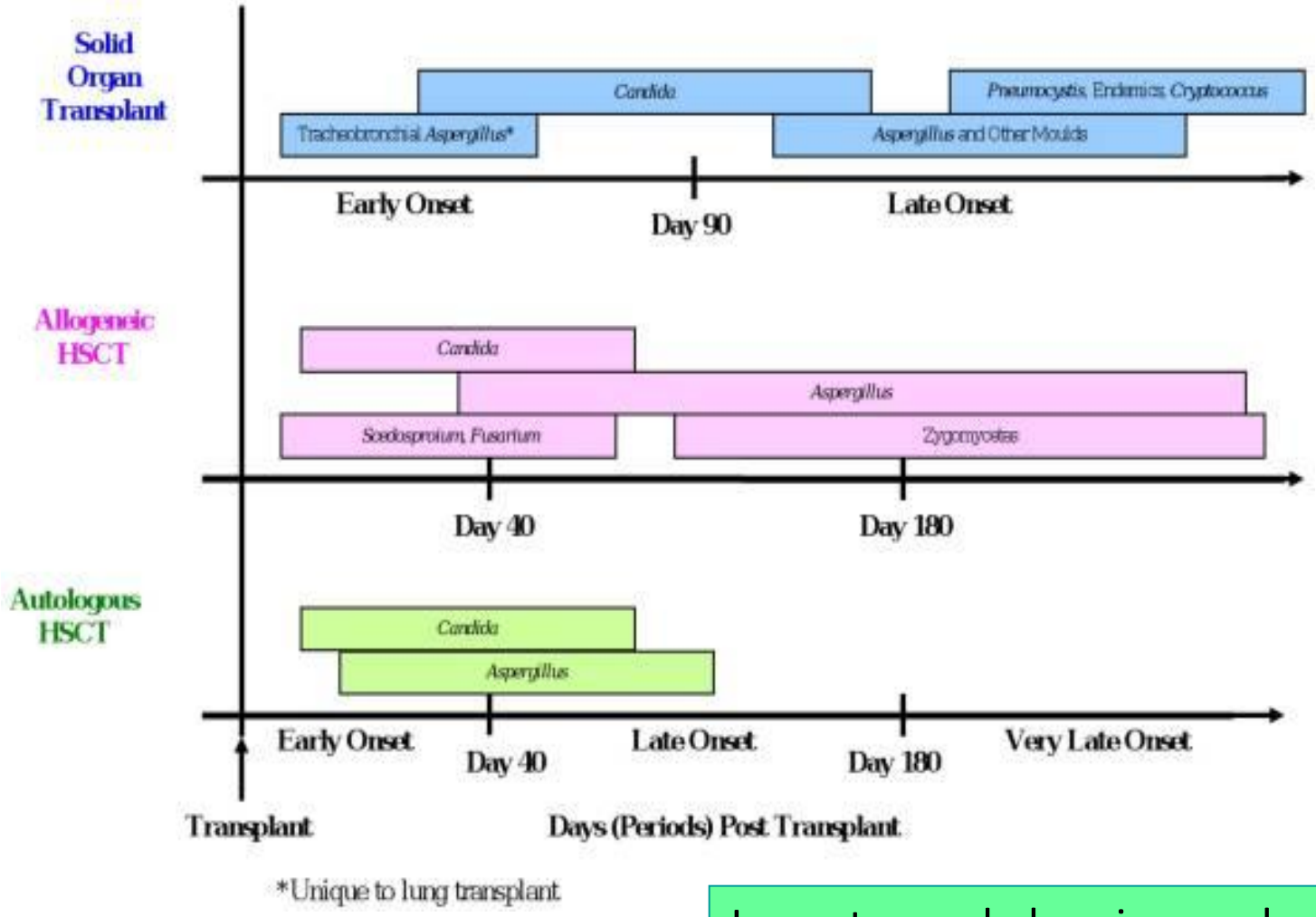
STP des Antifongiques?

- Analytique	
- Index thérapeutique étroit	efficacité (échec thérapeutique) sécurité (toxicité)
- Terrain à pronostic vital engagé	
- Variabilité PK	concentrations imprévisibles PGx adhérence au traitement
- Coprescriptions, IAM	

D'après Ensom MH

Individualisation de la thérapeutique AF?
Enjeu : détection changement concentration relevant au plan clinique

Moment de la survenue de l'IFI en fonction du type de transplantation



Person AK *Infect Dis Clin North Am* 2010

Importance de la prise en charge à la phase précoce

Importance des comorbidités

TABLE 2.

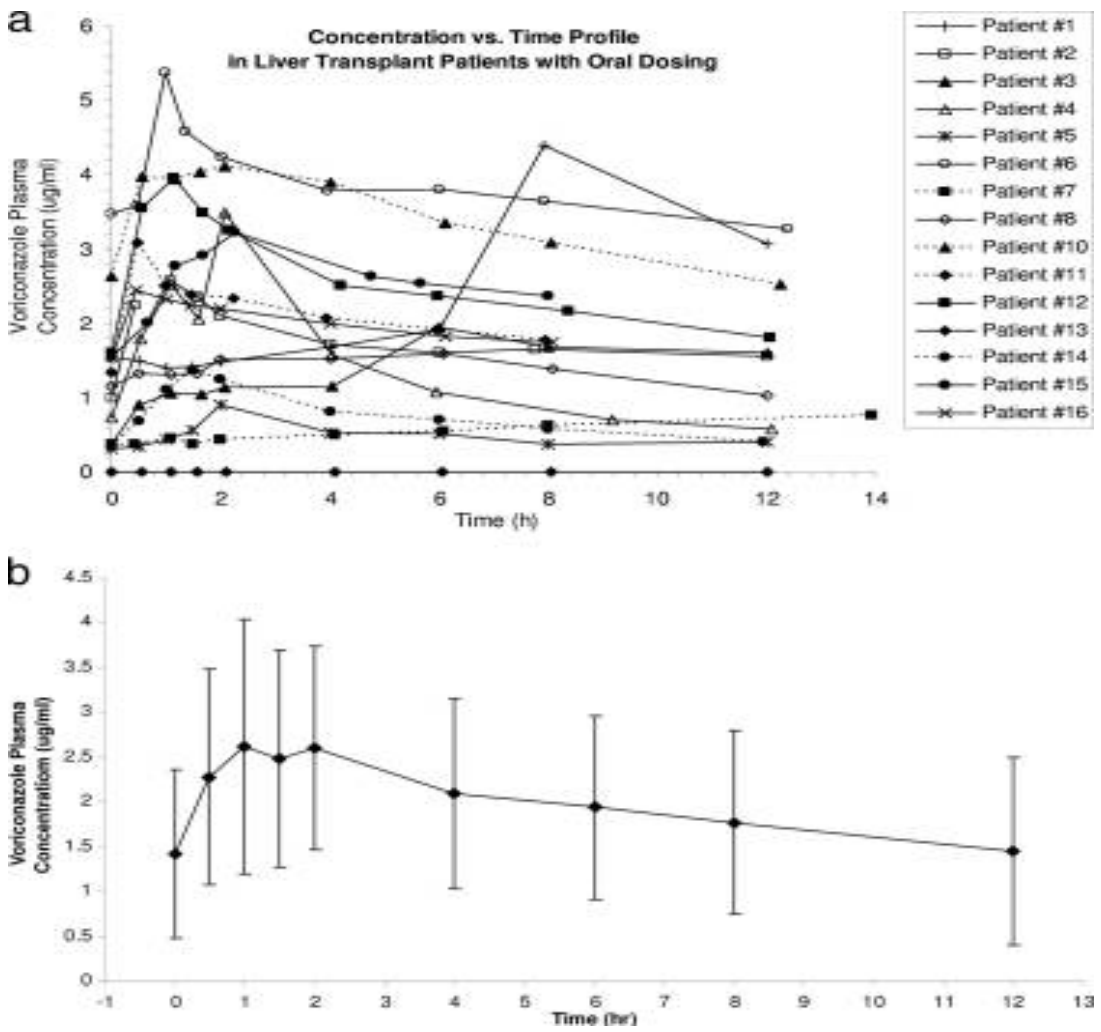
Variables portending a higher risk for invasive aspergillosis in transplant recipients[a]

Type of transplant and infection onset	Variables portending higher risk
Hematopoietic stem cell	
Early (within 40 days)	Cytomegalovirus disease, delayed neutrophil engraftment, alemtuzumab-containing conditioning regimen
Late (after 40 days)	Cytomegalovirus disease, T-cell-depleted or CD34-selected stem cells, unrelated or mismatched donor grafts, graft-versus-host disease, alemtuzumab for treatment of graft-versus-host disease, corticosteroid dose of >0.5 mg/kg/day
Liver	Retransplantation, renal failure (particularly requiring renal replacement therapy), fulminant hepatic failure as an indication for transplantation
[illegible]	Single lung transplant, cytomegalovirus infection, rejection and

Person AK *Infect Dis Clin North Am* 2010;

VRZ en Tx Hépatique : variabilté des concentrations
Prophylaxie orale 200 mg q12

Tx Hépatique



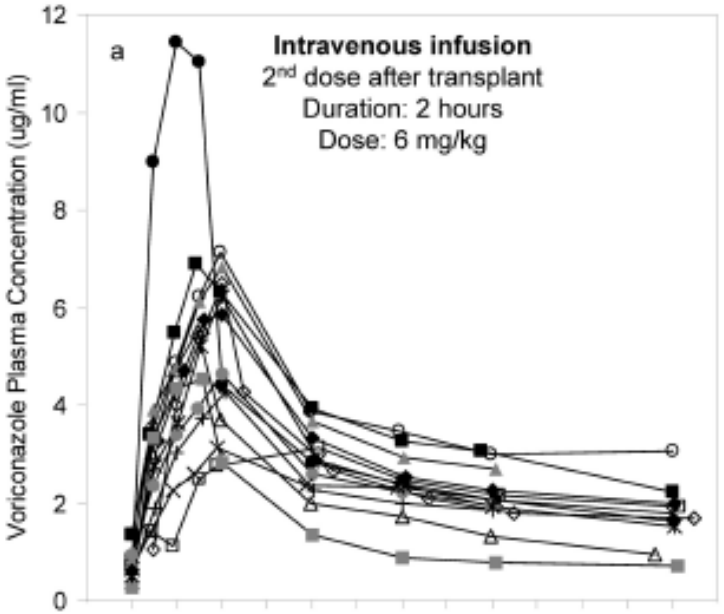
Johnson HJ *AAC* 2010

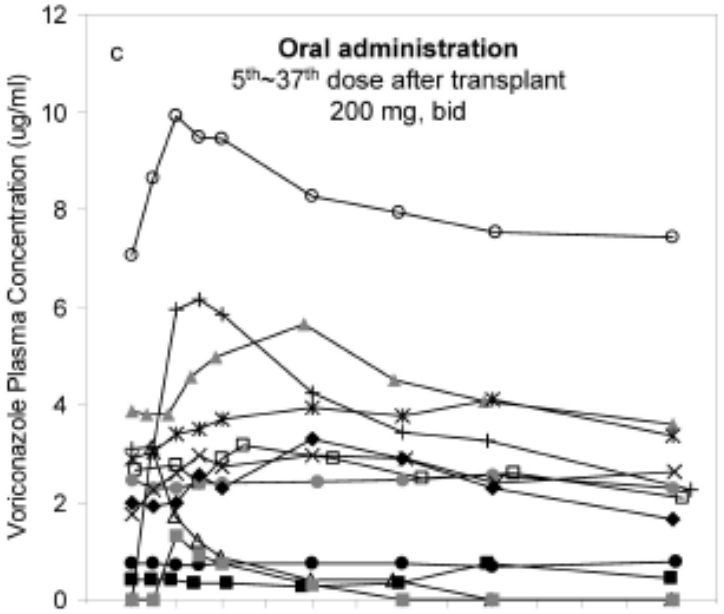
Tx Pulmonaire

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2010, p. 4426–4435 Vol. 54, No. 10
0066-4804/10/$12.00 doi:10.1128/AAC.00524-10

Bioavailability and Population Pharmacokinetics of Voriconazole in Lung Transplant Recipients[▽]

K. Han§§, B. Capitano,† R. Bies,‡§ B. A. Potoski, S. Husain,¶ S. Gilbert, D. L. Paterson,‖ K. McCurry,†† and R. Venkataramanan*





Han K *AAC* 2010

POUMON = organe cible infection opportuniste, Asp, CMV

Tx Pulmonaire

conazole pharmacokinetics was demonstrated. Bioavailability of voriconazole is substantially lower in lung transplant patients (45.9%) than non-transplant subjects (96%) but increased significantly with postoperative time, likely due to recovery of gastrointestinal functions. Exposure and bioavailability of voriconazole are significantly lower in CF patients, likely due to impaired absorption of voriconazole caused by physiological changes associated with CF. We rec-

Han K *AAC*

CF = fréquente colonisation pré-Tx et exposition aux AF

Tx PULMONAIRE, notamment CF :

Prophylaxie primaire du greffon
mais secondaire du patient

chez un receveur immunodéprimé,
A considérer comme un enjeu CURATIF

<u>Modifications du terrain mucoviscidose (CF)</u> :

risque de **sous-exposition** médicamenteuse
et de **toxicités** additionnelles

- clairances reliées au plus jeune âge
- GERD, fonction digestive
- variabilité PK augmentée
- coprescriptions nombreuses

Billaud EM *Med Myc,* 2010

Tx Pulmonaire, mucoviscidose

	PSZ CF/LTx	
	EP	LP
n	14	14
Dose (mg/d)	800	950
C0 ± SD (mg/	**0,8 ± 0,7**	**1,0 ± 0,4**

	VRZ CF/LTx	
	EP	LP
n	29	29
Dose		
C0 ± SD	**1,5 ± 1,0**	**0,9 ± 1,0**

	PSZ LK/BMTx	
	EP	LP
n	13	9
Dose	600	600
C0 ± SD	**0,54 ± 0,36**	**0,55 ± 0,51**

	VRZ LK/BMTx	
	EP	LP
n	8	7
Dose	445	430
C0 ± SD	**2,4 ± 1,8**	**1,7 ± 1,3**

EP = early phase (D8) LP = Late phase (M1)

Cf [Lebeaux, 2009] Hématologie

Exposition faible et variable en PSZ/ pédiatrie, mucite et diarrhée

Spécificités

Localisation

passages intracellulaire, intra-pulmonaire démontrés

La question:

Apport du STP pour conduire une augmentation de dose en cas de localisation profonde

comme une endocphtalmite fongique? [Spriet I *JAC* 2009]

Spécificités

Pathogènes

Ex: Scedosporium sp

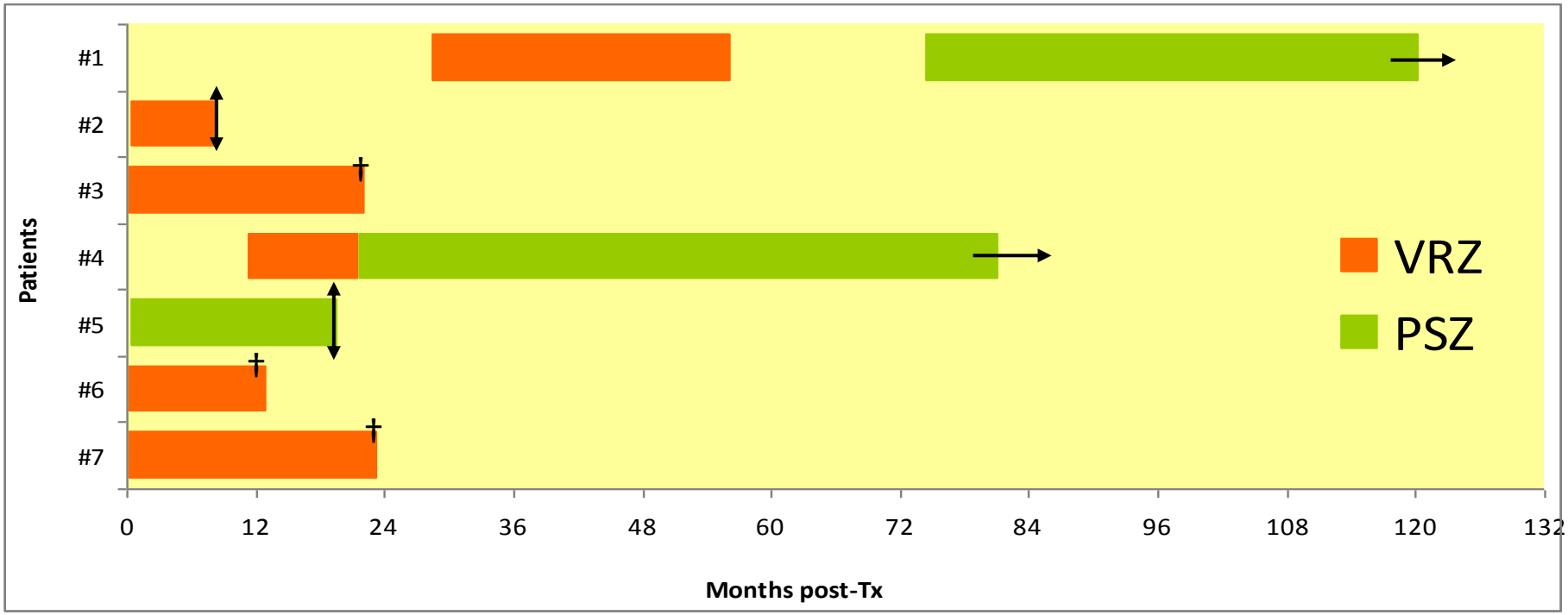
Associé à un pronostic très péjoratif /ID [Morio F, 2010]

Considéré usuellement comme une contre-indication à la Tx

Working group - Fungal respiratory infections in CF-Angers – 1st/2nd September 2011

Case series (8) CFLTx with *Scedosporium sp*

- The seven colonized patients were treated with VRZ (n=6) or PSZ (n=3)
- VRZ was stopped in 3 cases, 2 switch to PSZ
- AF therapy interrupted in 3 situations : success, complications, compliance



STP des azoles

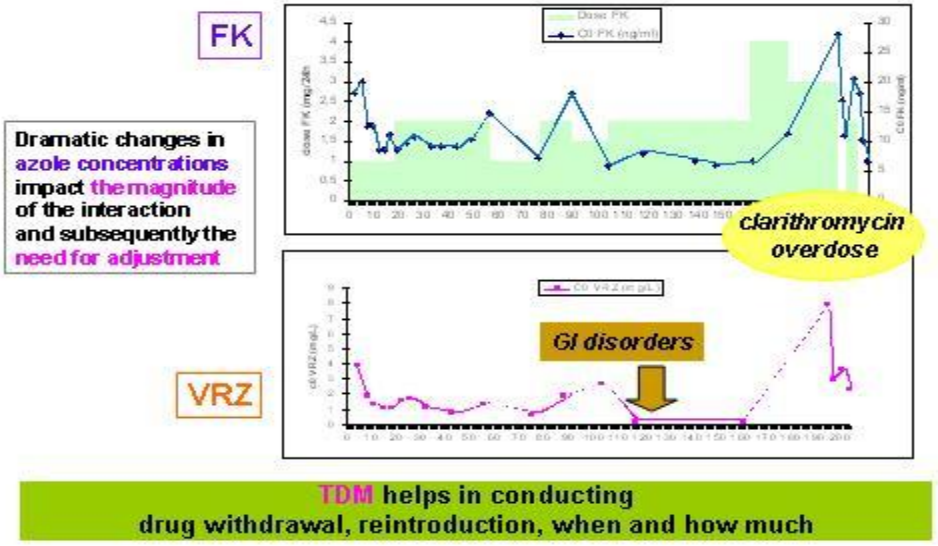
IATDMCT 2011 # 143

ISHAM FRICF
Fungal respiratory infections in cystic fibrosis

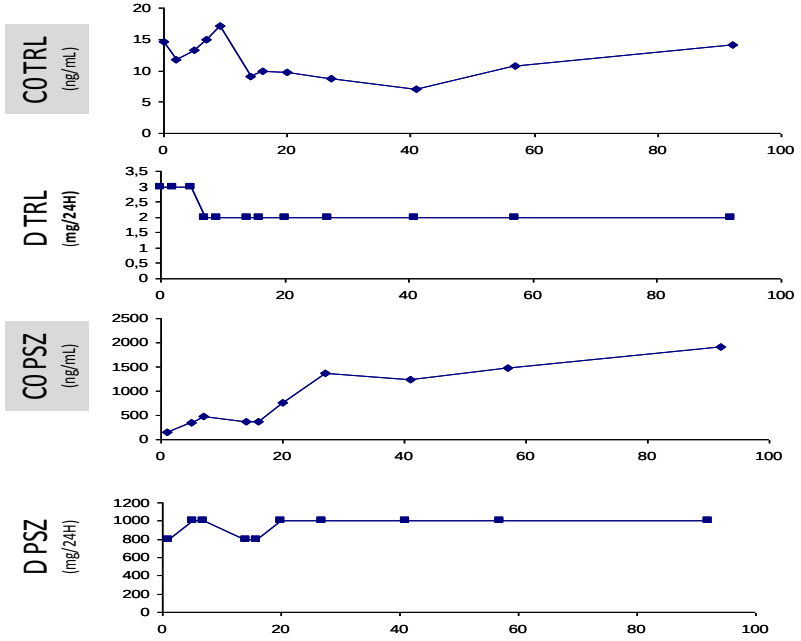
- **C0 plasmatiques moyens acceptables à**
  - **1.4 ± 0.7 mg/L (VRZ)**
  - **0.8 ± 0.6 mg/L (PSZ)**

Doses d'entretien moyennes
VRZ 530 ± 174 mg/j (+43%)
PSZ 1550 ± 638 mg/j (+200%)

Interaction VRZ – FK : JOINT TDM



Examples of combined TDM of PSZ and tacrolimus (TRL)



Due to azole pharmacokinetic variability in CFLTx patients, the steady-state is longer to reach, and higher dosages with careful TDM are needed to achieve appropriate therapeutic efficacy and safe immunosuppressive drug-drug interactions

EMB IATDMCT 2011 Stuttgart S7

Spécificités

Pédiatrie

Prendre en compte la classe d'âge

NN
2-12 ans
12-18 ans

et le POIDS

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2010, p. 4116–4123 Vol. 54, No. 10
0066-4804/10/$12.00 doi:10.1128/AAC.00896-10

Pharmacokinetics, Safety, and Tolerability of Voriconazole in Immunocompromised Children[▽]

Thomas J. Walsh,[1,2]* Timothy Driscoll,[3] Peter A. Milligan,[4] Nolan D. Wood,[5] Haran Schlamm,[4,5] Andreas H. Groll,[6] Hasan Jafri,[7] Antonio C. Arrieta,[8] Nigel J. Klein,[9] and Irja Lutsar[4,10]†

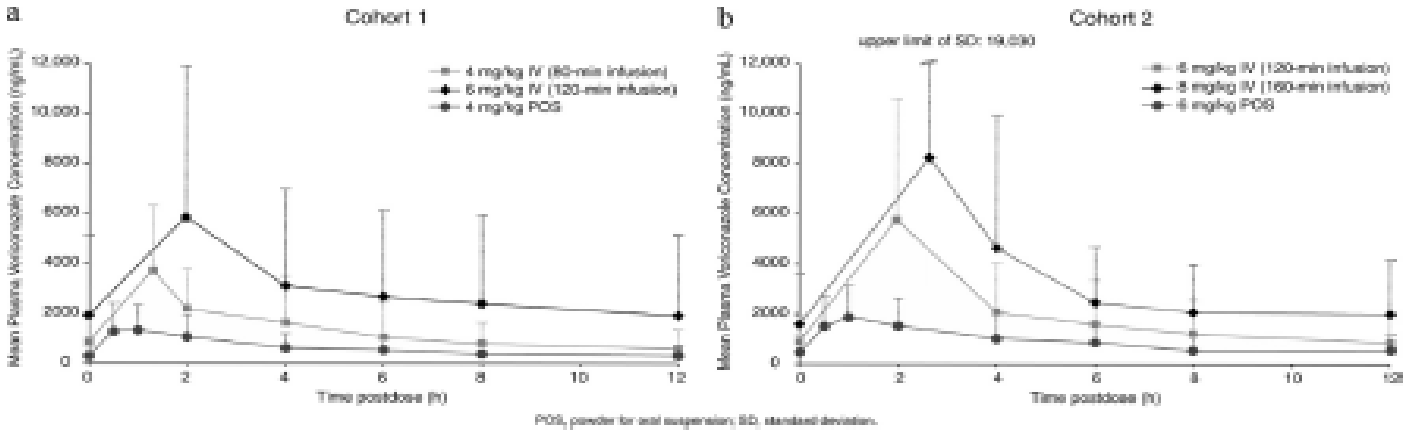


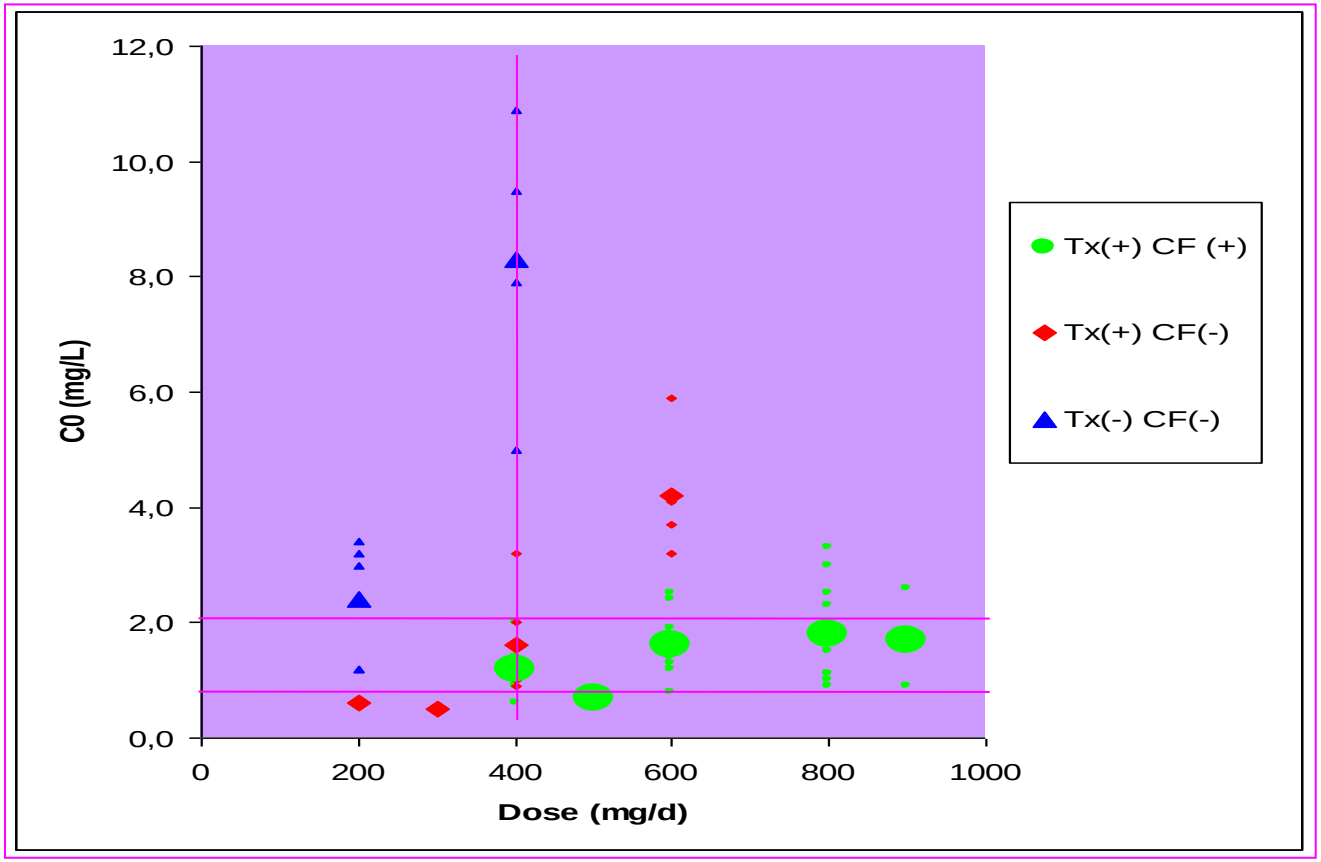
FIG. 1. Mean plasma voriconazole concentrations in cohort 1 (a) and cohort 2 (b).

8 mg/kg I.V. q12 children ~ 4 mg/kg I.V. q12 adults

WalshTJ *AAC 2010*

VRZ : C0 selon la dose et le type de patient

[Imhof 2006, Pascual 2008, Berge, 2009]



La dose nécessaire pour atteindre des concentrations de VRZ thérapeutiques en CF Tx (●)

Est en moyenne plus haute and plus variable par rapport aux patients trnasplantés non CF(◆) ou non transplantés (♦).

Adaptations conduites > 800 mg/j nécessaires pour atteindre concentrations détectables

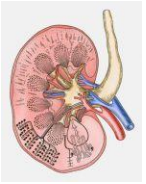
Interactions IAM

PK CYP3A4-Pgp targets
such as IS drugs but also voriconazole, oral contraceptives and anticoagulants

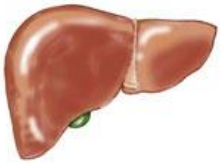
	Inhibitors ↑ [target drug]	*Inducers* ↓ [target drug]
ARV PI	***PROTEASE INHIBITORs*** ***ritonavir (/r)***	***RIFAMPICIN***
	AZOLES ***ketoconazole itraconazole voriconazole posaconazole fluconazole isavuconazole?***	**ANTICONVULSIVANTS** **phenobarbital phenytoine**
	MACROLIDES ***erythromycine clarithromycin josamycin...***	**QT prolongation** **rhabdomyolisis and metabolised statins**
	CALCIC INHIBITORS **nicardipine diltiazem**	**Herbal** **St John's wort**
	target	CsA < TRL < ERL < SRL — **IS**

PD
Toxicities

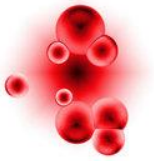
NEPHROTOXICITY
amphotericin B
aminosides
colistin
cotrimoxazole (oral)
calcineurin inhibitors



HEPATOTOXICITY
Azoles (ketoconazole, voriconazole)
isoniazide



HAEMATOTOXICITY
ganciclovir
antiretrovirals
ribavirin
mycophenolic acid
mTOR inhibitors



NEUROTOXICITY
didanosine
aciclovir
voriconazole
colistin

inhibiteurs (azoles) et cibles (VRZ, ITZ)

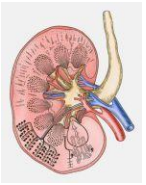
P3A4-Pgp targets
drugs but also voriconazole,
ontraceptives and anticoagulants

Inhibitors ↑ [target drug]	*Inducers* ↓ [target drug]
PROTEASE INHIBITORs ***ritonavir (/r)***	***RIFAMPICIN***
AZOLES ***ketoconazole itraconazole voriconazole posaconazole fluconazole isavuconazole?***	**ANTICONVULSIVANTS** **phenobarbital phenytoine**
MACROLIDES ***erythromycine clarithromycin josamycin...***	**QT prolongation** **rhabdomyolisis and metabolised statins**
CALCIC INHIBITORS **nicardipine diltiazem**	**Herbal St John's wort**
Grapefruit juice	

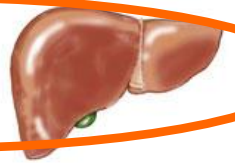
target CsA < TRL < ERL < SRL

PD
Toxicities

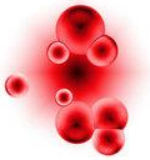
NEPHROTOXICITY
amphotericin B
aminosides
colistin
cotrimoxazole (oral)
calcineurin inhibitors



HEPATOTOXICITY
Azoles (ketoconazole, voriconazole)
isoniazide



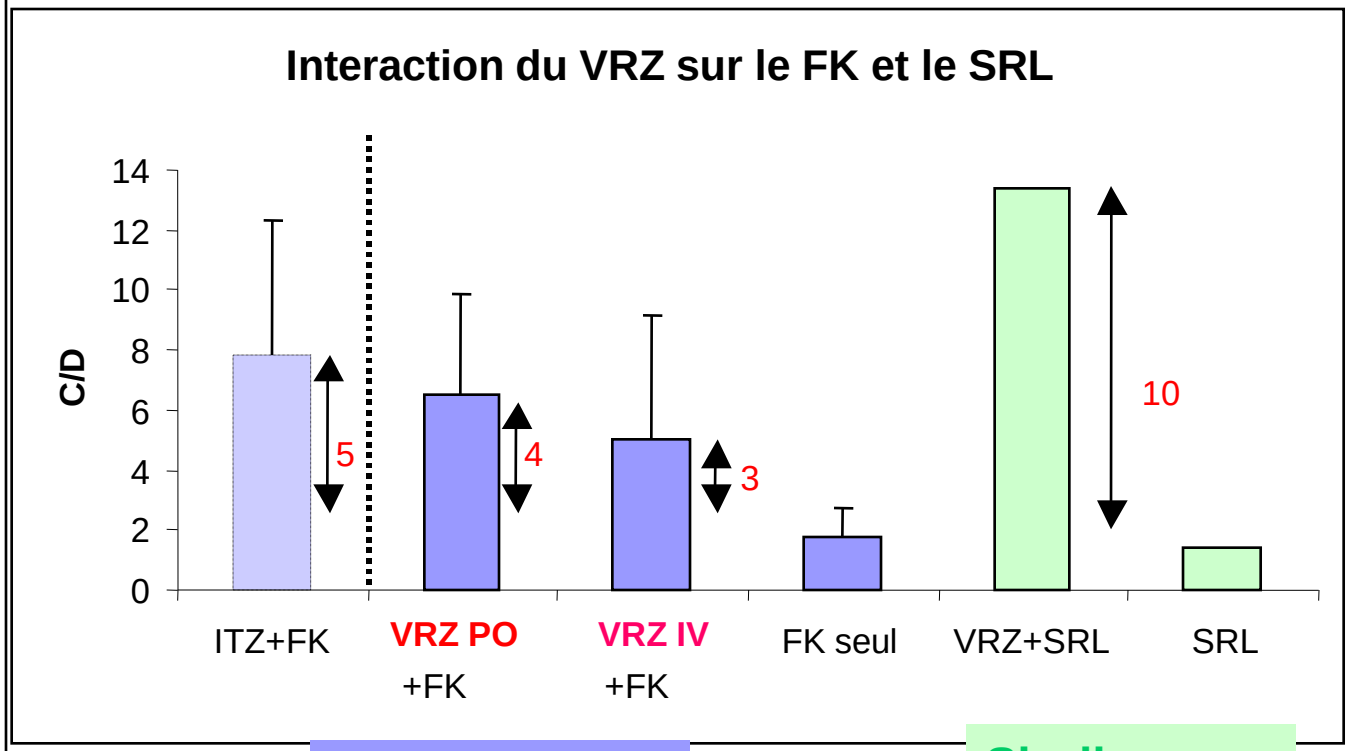
HAEMATOTOXICITY
ganciclovir
antiretrovirals
ribavirin
mycophenolic acid
mTOR inhibitors



NEUROTOXICITY
didanosine
aciclovir
voriconazole
colistin

Interactions, aspects quantitatifs

Interactions azolés : VRZ / IS



[Berge M TID 2009]

Interactions, aspects quantitatifs

Interaction azolés - IS

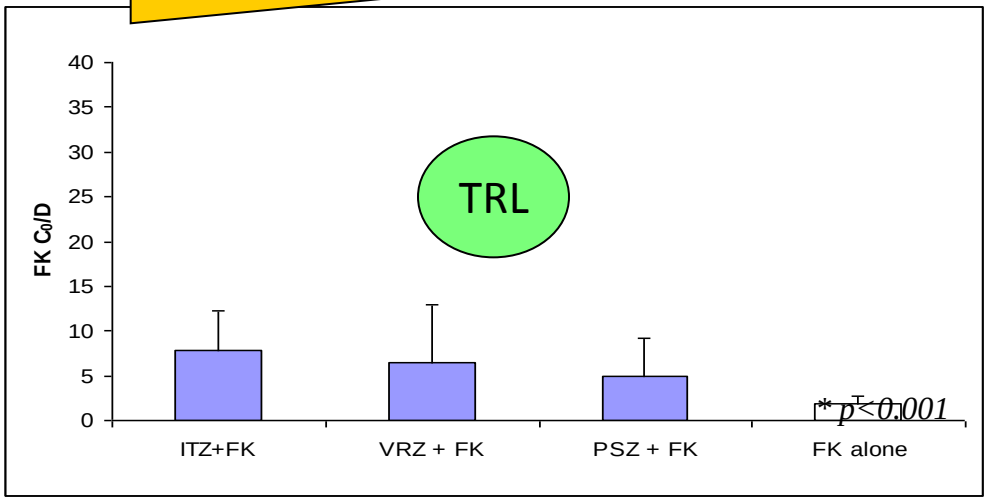
ITZ > VRZ ~ PSZ

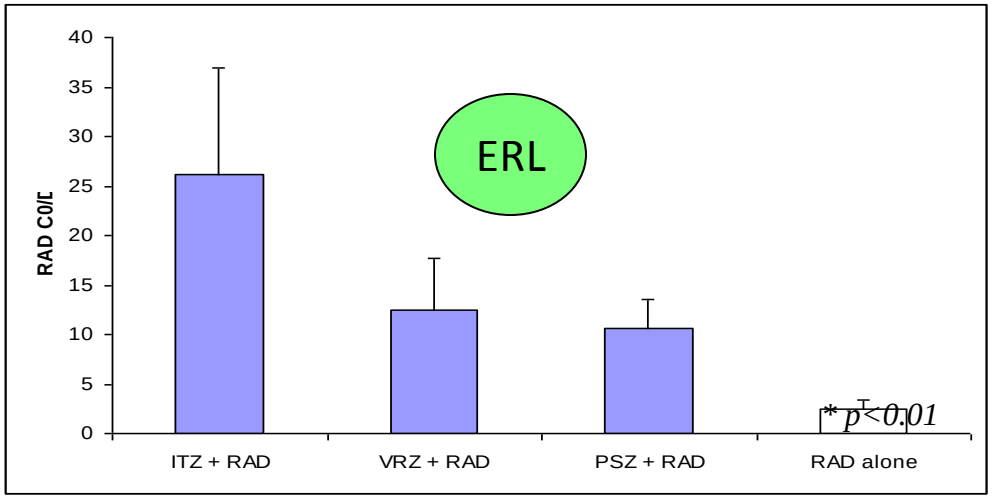
Azole-IS IAM

TRL

PK

ERL





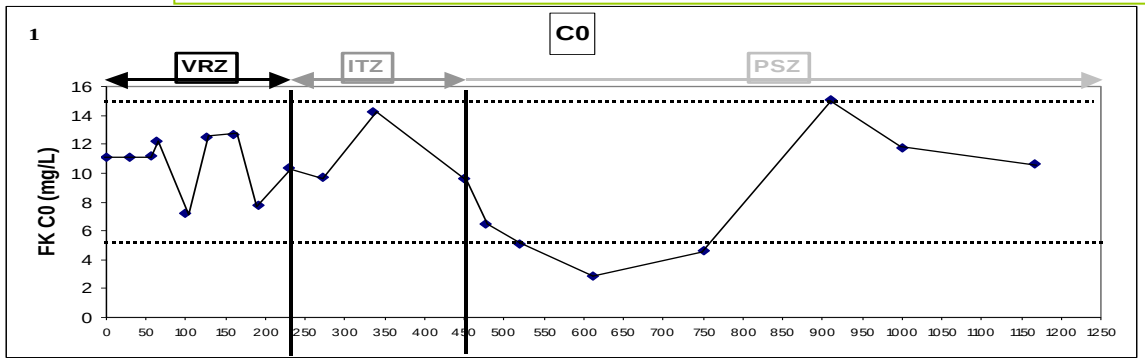
TRL

PD

ERL

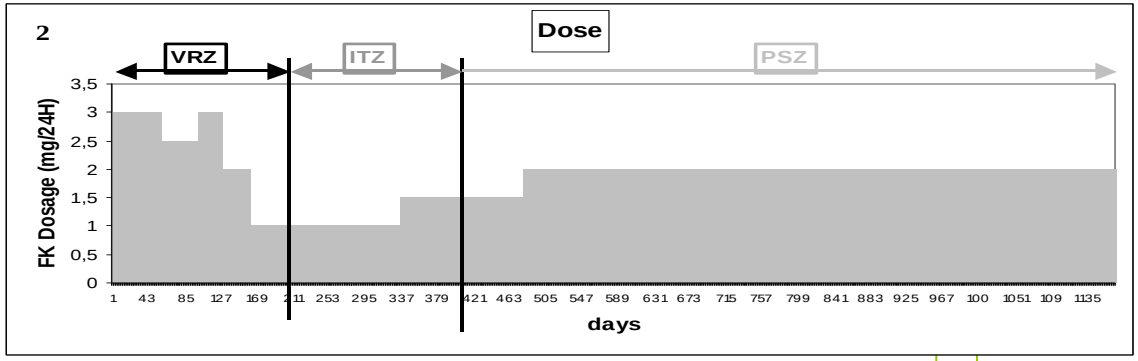
Conséquences cliniques

Individual TDM basis DDI management : switch and withdrawal

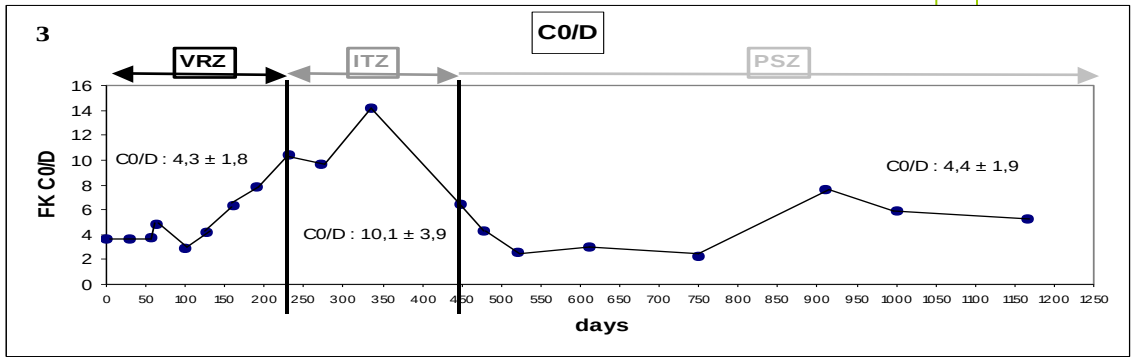


FK Therapeutic drug monitoring in a lung transplant patient with cystic fibrosis during three different consecutive azoles therapy

VRZ then ITZ then PSZ



No dramatic change in FK C0

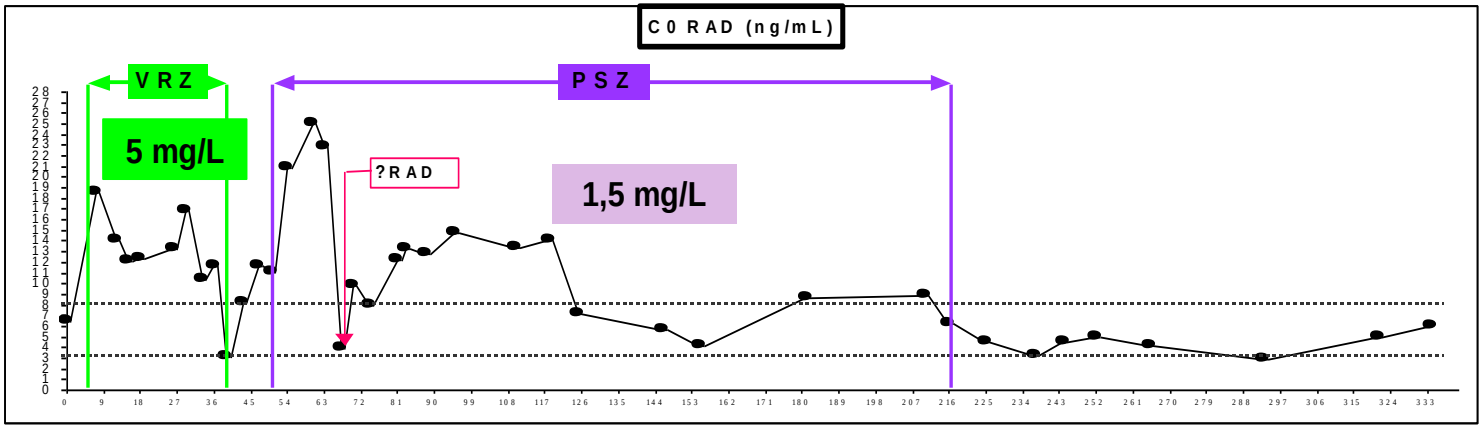


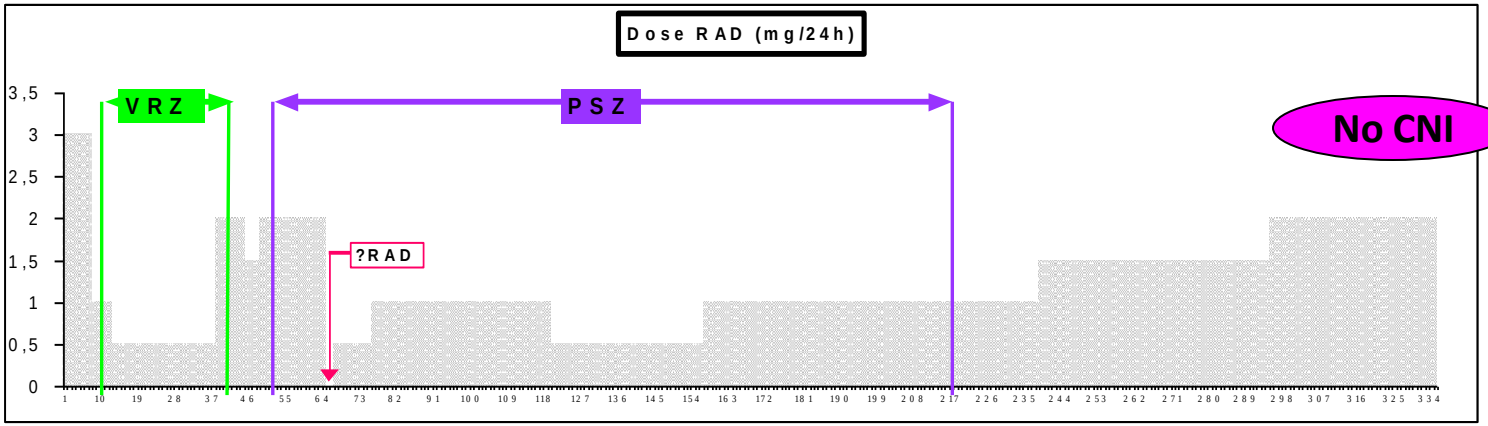
Difference of inhibition on FK metabolism between azoles

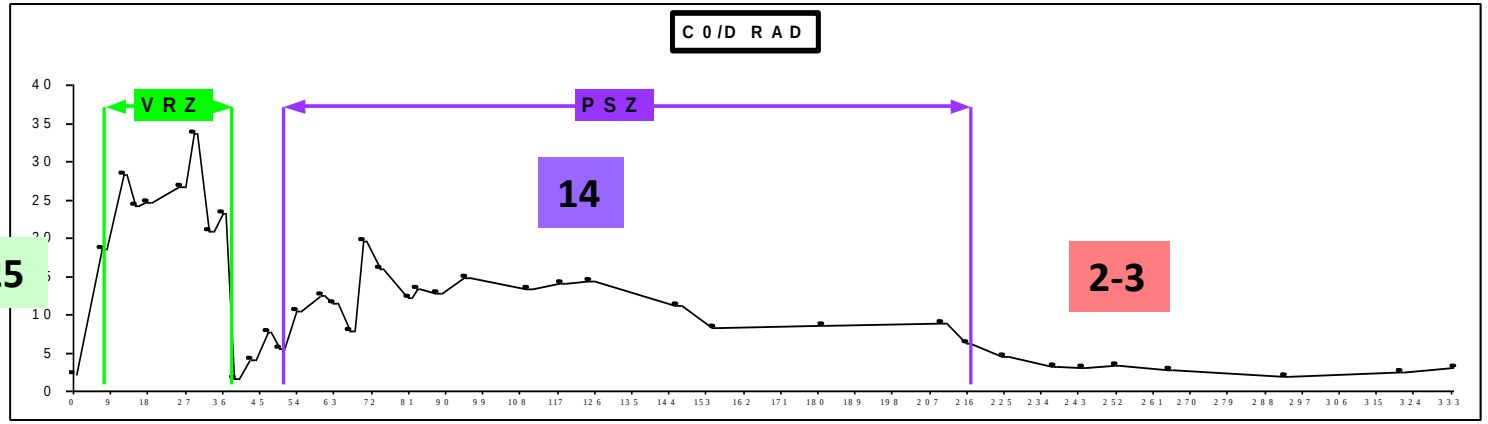
ITZ > VRZ ≥ PSZ

Tx Rénal
RAD /Azolés

CDI 2009

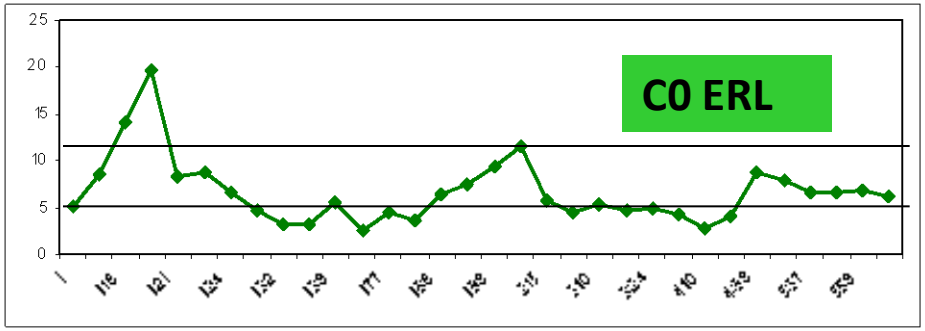


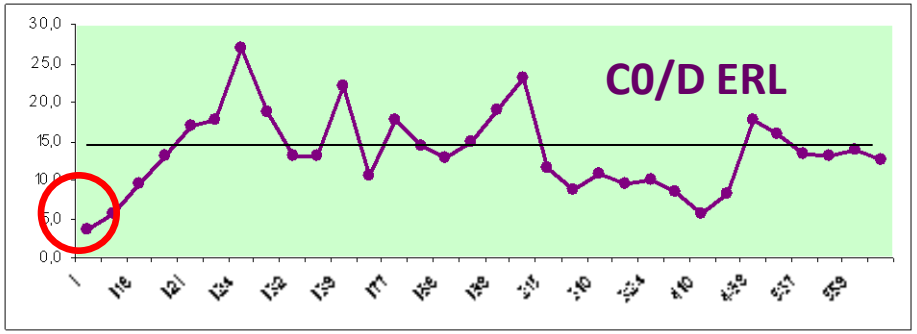


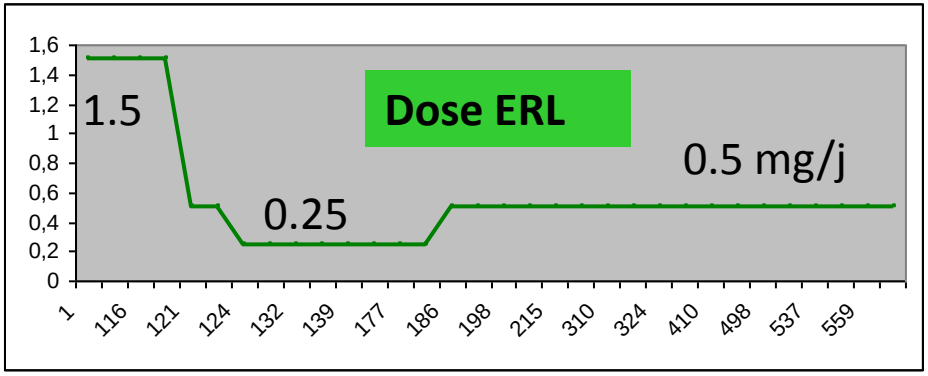


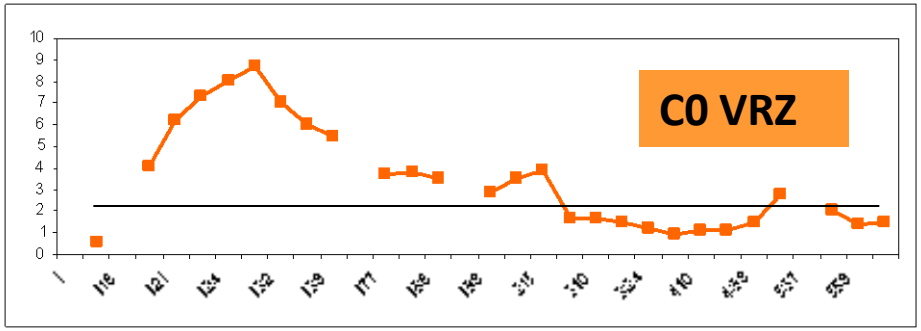
Calm R, 61 ans, TxH
VRZ / ERL

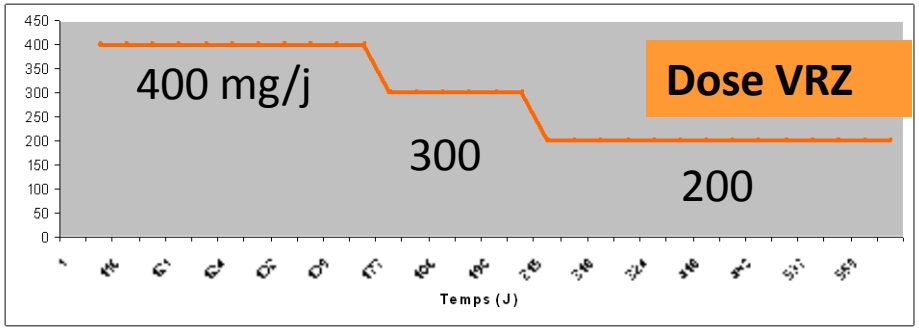
[Pea F Ann Pharmacother 2008]
1 cas d'interaction VRZ – ERL
Chez un TxH, décédé











Bolus SMD / TRL et VRZ TxP CF

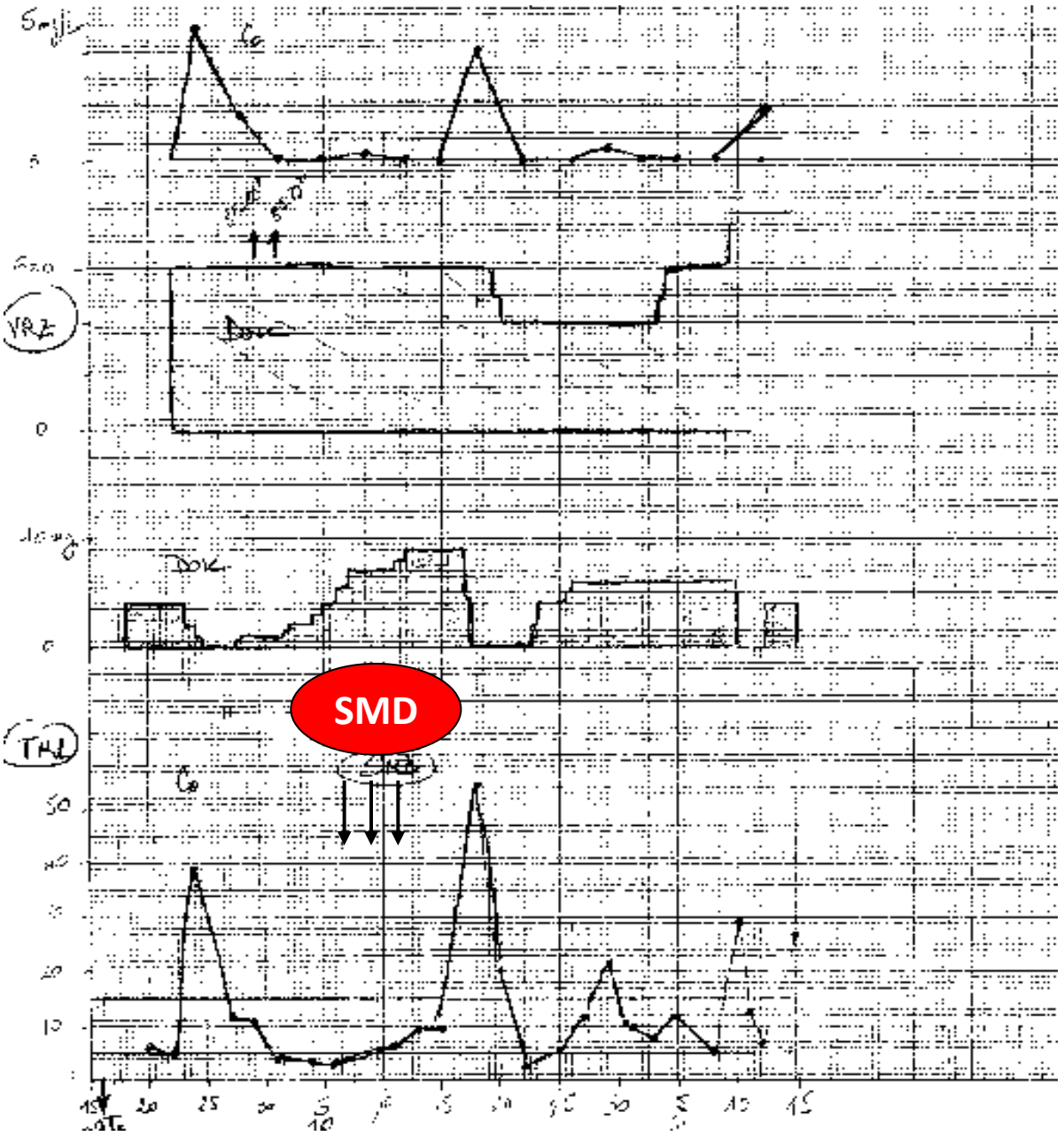
C0 VRZ

Dose VRZ

Dose TRL

SMD

C0 TRL



IAM : IPP et Azolés

IPP, métabolisme et VRZ

tous ne relèvent pas du même schéma métabolique

il faudrait donc les considérer un à un en terme de profil métabolique

IPP, pH et absorption du PSZ

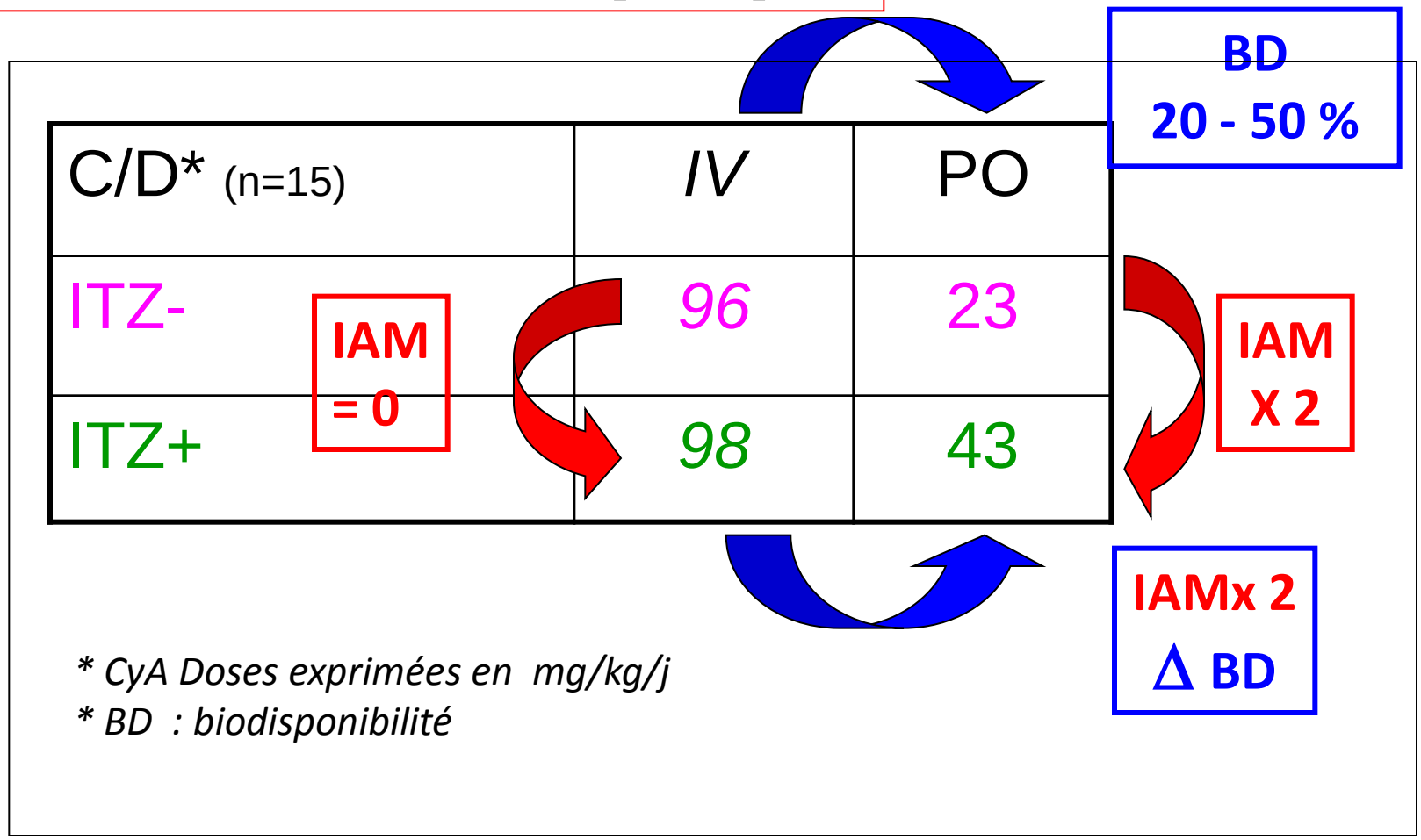
ces médicaments sont supposés améliorer la fonction digestive

Éventuellement y compris l'absorption du PSZ

Rôle de la voie d'administration
CYP3A4 / Pgp = hépatique + intestinal

ΔBD +IAM

CyA ratio C0/Dose durant ITZ coprescription



[Yokomasu 2009] étude chez le rat : pas d'interaction sur ERL IV avec ITZ vs PO

Zaragoza R *2008*

Therapeutics and Clinical Risk Management 2008:4(6) 1261–1280

Multidisciplinary approach to the treatment of invasive fungal infections in adult patients. Prophylaxis, empirical, preemptive or targeted therapy, which is the best in the different hosts?

Abstract: The high morbidity, mortality, and health care costs associated with invasive fungal infections, especially in the critical care setting and immunocompromised host, have made it an excellent target for prophylactic, empiric, and preemptive therapy interventions principally based on early identification of risk factors. Early diagnosis and treatment are associated with a better prognosis. In the last years there have been important developments in antifungal pharmacotherapy. An approach to the new diagnosis tools in the clinical mycology laboratory and an analysis of the use new antifungal agents and its application in different clinical situations has been made. Furthermore, an attempt of developing a state of the art in each clinical scenario (critically ill, hematological, and solid organ transplant patients) has been performed, trying to choose the best strategy for each clinical situation (prophylaxis, pre-emptive, empirical, or targeted therapy). The high mortality rates in these settings make mandatory the application of early de-escalation therapy in critically ill patients with fungal infection. In addition, the possibility of antifungal combination therapy might be considered in solid organ transplant and hematological patients.

Plusieurs développements récents en parallèle

Zaragoza et al

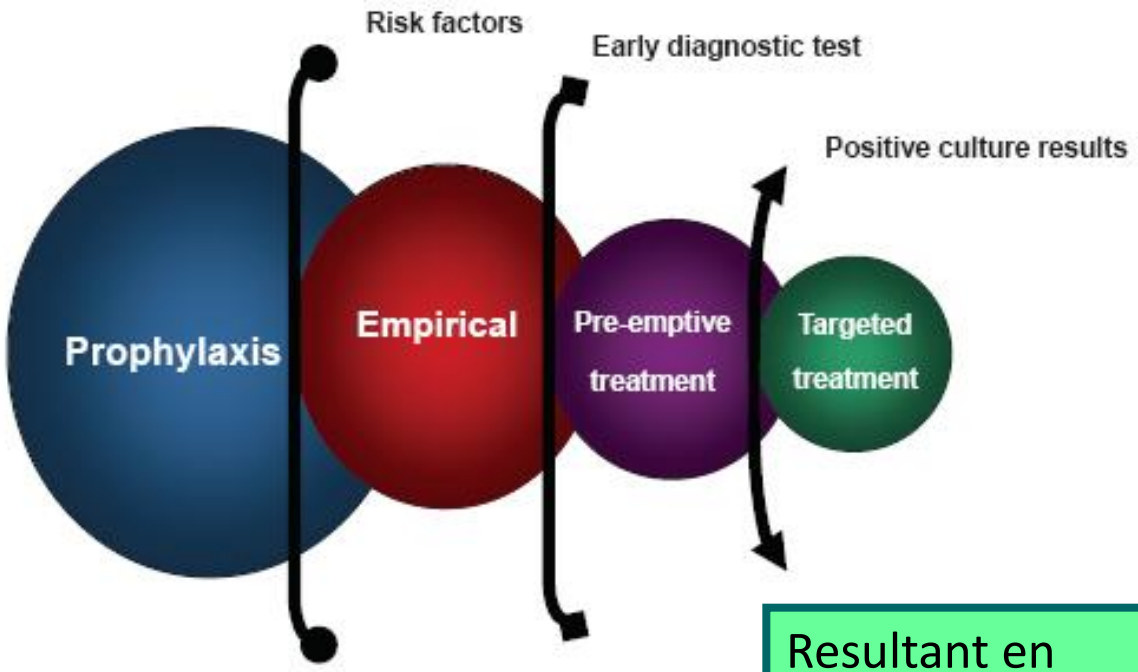


Figure 1 Different antifungal strategies for treatment in invasive fungal infections based on diagnostic stage.

Resultant en
une épidémiologie différente
et différences ds strategies AF

Zaragoza R 2008

Antifungal TDM evidence and concentration targets: 2011

Goodwin ML & Drew RH *JAC* 2008, revisited

Table 1. Summary of data supporting the application of serum concentration monitoring for newer antifungal agents

Medication	Serum concentration monitoring recommended	Peak	Trough	Comment
Amphotericin B	no	n/a	n/a	
Flucytosine	yes	2 h post-dose: 30–80 mg/L for cryptococcal infections; 40–60 mg/L for candidal meningitis	n/a	toxicity seen with 2 h post-dose concentrations >100 mg/L
Fluconazole	sometimes	n/a	n/a	
Itraconazole	yes	n/a	>0.5 to 1 mg/L	to ensure adequate absorption
Voriconazole	yes[a]	<6 mg/L	>2 mg/L	to ensure efficacy, limit toxicity
Posaconazole	?	>1.48 mg/L[b]	0.5-0.7	limited data, average concentration of 1.25 mg/L associated with 75% response[b]
Caspofungin, micafungin and anidulafungin	maybe	n/a	n/a	

[a]Consider (when available) in 'non-responders', questionable medication compliance, significant drug–drug interactions, suspected toxicity.
[b]Data based on treatment of *Aspergillus* with posaconazole.

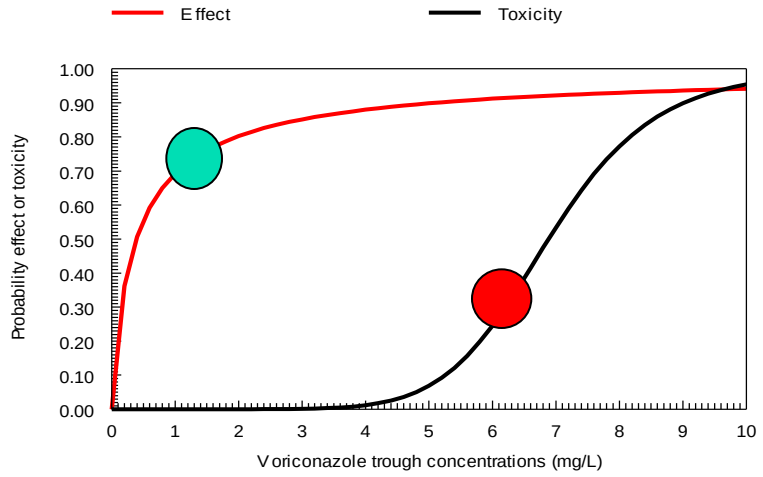
VRZ C0<3-4

Imhof; Boussaud V *JHLT* 2008; Myakis S *Clin Microbiol Infect Dis* 2010

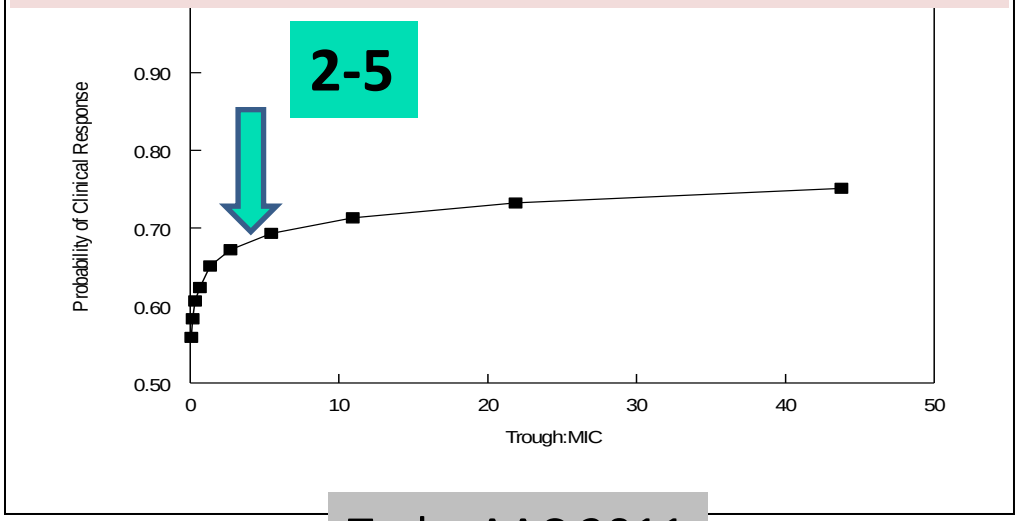
≠ VRZ C0 < 6mg/L Andes *D 2009*.

Trough : MIC as a therapeutic target

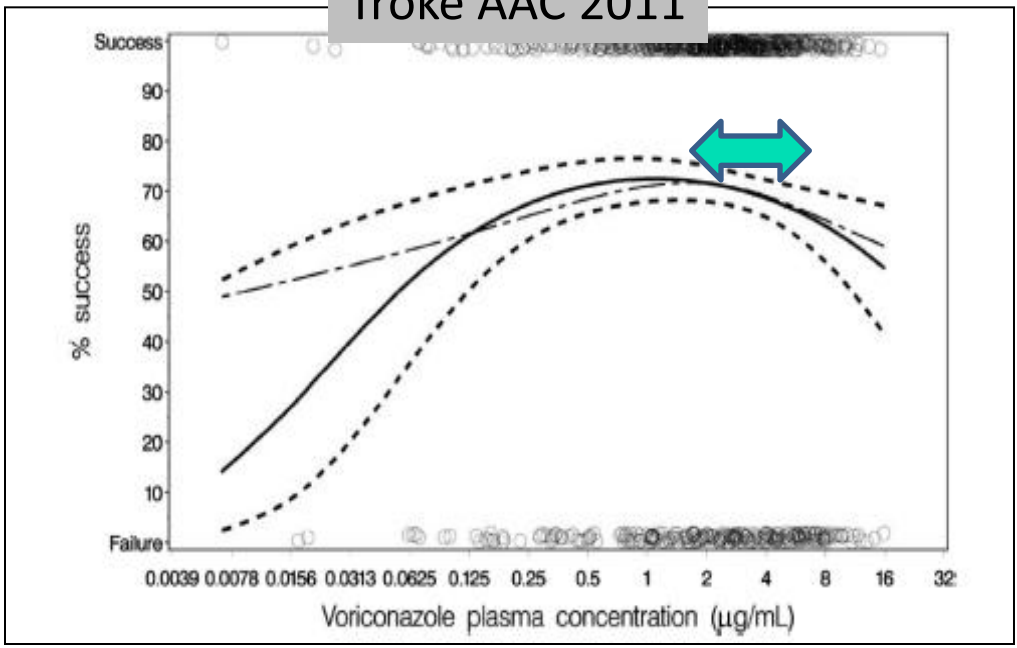
VRZ : relation concentration-effect & concentration-toxicity



Pascual et al CID 2008



Troke AAC 2011



D'après W Hope, IATDMCT 2011

combinaison AF

On PK basis

The high risk of inefficacy during underdosed periods was supplied by the use of
antifungal associations, specially with caspofungin,

[Marr 2004]
[Singh 2006]

supported by an
individualized concentration-controlled adaptation,
waiting for (VRZ) documented concentration

Berge M *TID* 2009

PK = N, pas S «condition nécessaire, pas suffisante»

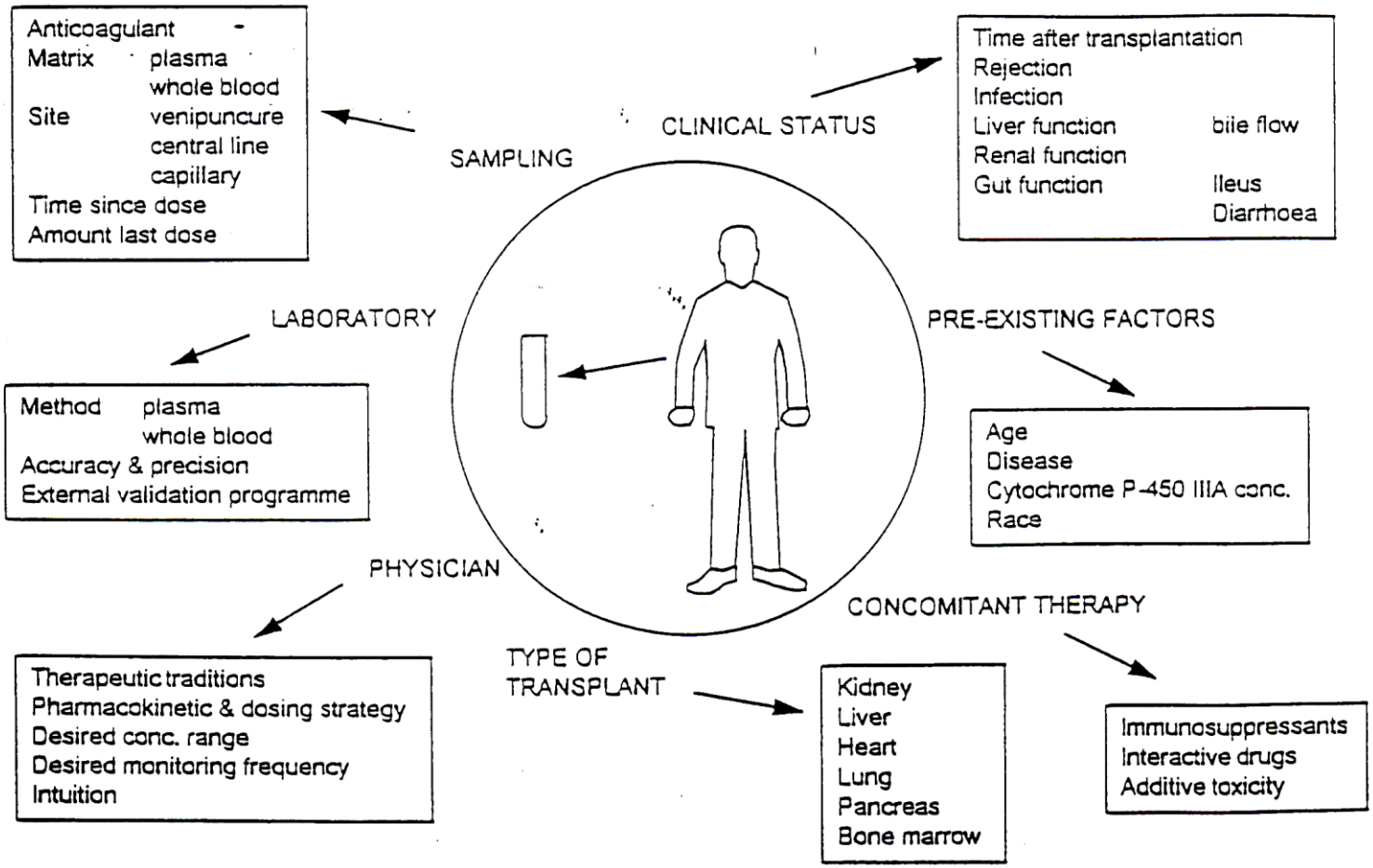
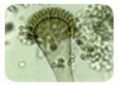


FIG. 1. Some points of consideration when evaluating an immunosuppressive drug sample.

Ther Drug Monit, Vol. 17, No. 6, 1995

Conclusions


STP Conclusion (2) : niveau de preuve

A lot of reviews [Smith and Andes, 2009; Hope 2008…]
Valuable recommendations [Walsh 2008, Singh and Husain, 2009]
Few studies, most of them retrospective series

Mais évidence émergente, au moins pour populations spéciales heureusement très représentatives

CF, haemato	GERD, mucositis	pediatrics	low exposure
Ageing	Hepatic insufficiency (PK) higher sensitivation (PD)		high exposure high toxicity
Underlying	Tx, BMT, HIV BK		DDI +++
Long course	compliance, steady-state control		

STP **besoin d'études <u>collaboratives</u> prospectives…..certes mais déjà utilisé et utile….OUI**

Tendance

- STP pleinement reconnu en Infectiologie, avec des essais appropriés
- Nombreuses publications avec toujours beaucoup de revues
  mais plus de data originaux, confortant perception initiale du management AF

Généralités qui s'appliquent aux médicaments AF

- Effet de l'âge sur la clairance
- Pathologie sous-jacente, désordres digestives et absorption

Considérations spécifiques liées à l'AF

VRZ le plus de challenges

- en terme d'index thérapeutique (faible exposition, même IV), tolérance
- cible d'interactions
  STP joint pour gérer les aspects quantitatifs de leurs interactions
- mais positif en curatif (voie IV , dose de charge)
  Difficile à maintenir au long cours (photosensbilisation)

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PSZ - Prophylaxie
court-terme (hématologie): besoins en STP limités, détection des ss-dosages
entretien au long cours : Scedo +

- moins adapté au ttt curatif (sauf justification PD)

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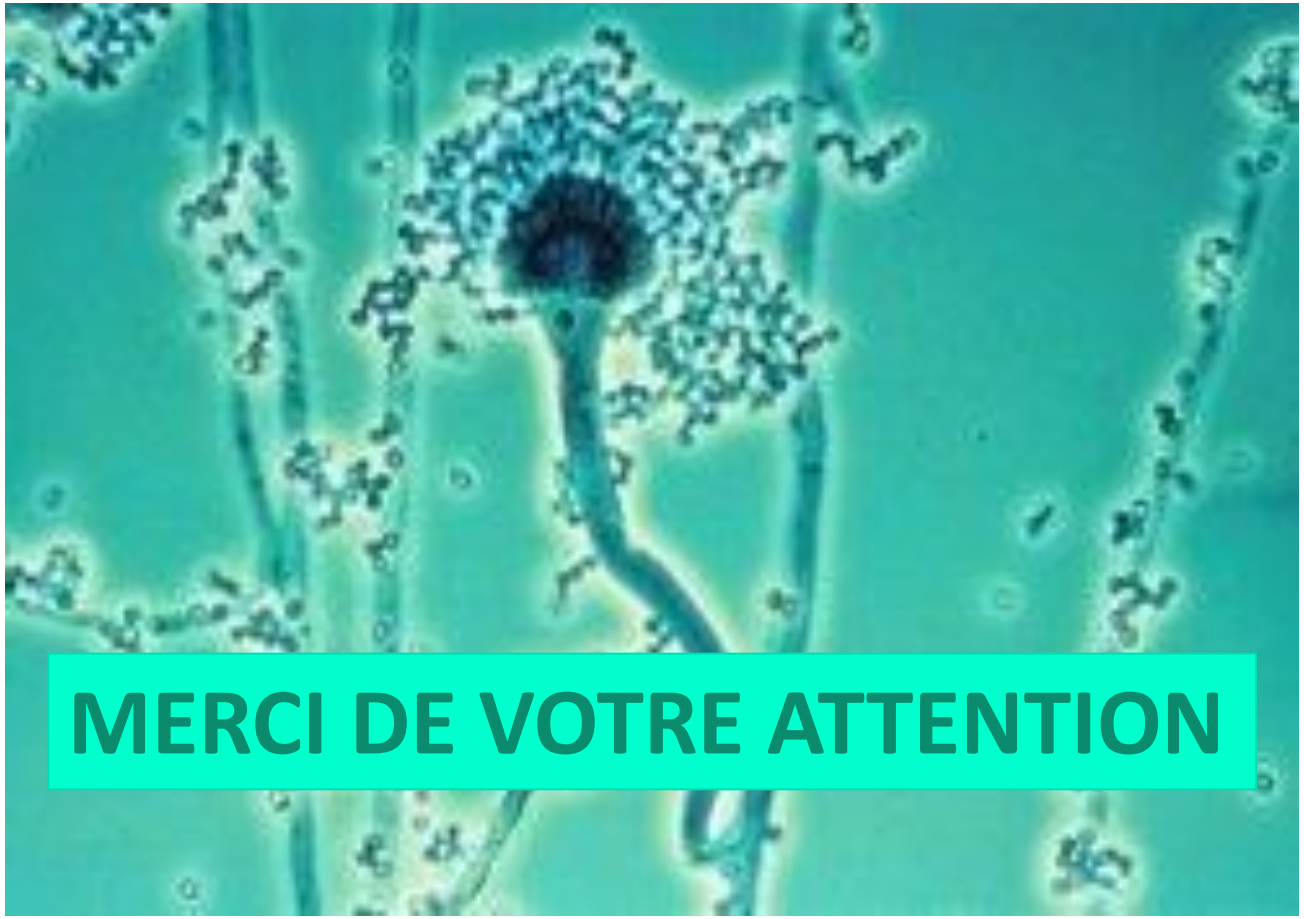
Echinocandins (Caspofungin)

- escalade de dose dans un sous-groupe de patients et situations?


MERCI DE VOTRE ATTENTION

Titre de la slide

- Texte
  - Texte
    - Texte
- Texte
  - Texte
    - texte

The Echinocandins

The question:

Is there any benefit of caspofungine dose-escalation?
In a TDM-based approach for a large therapeutic index drug?

That is:

- Reality of the 1mg/L threshold target [Bartizal K 1997]

- Benefit to increase dosage, targeting overexposure to overcome
  * emerging problems of resistance
  * localisations hardly achievable

- Benefit to increase dosage, to overcome documented underexposure
  * Intensive Care

A phase II dose escalation study of caspofungin for invasive aspergillosis

Cornely OA(*)[1,2,3,4], Vehreschild JJ(*)[1], Vehreschild MJGT[1], Würthwein G[5], Arenz D[2], Schwartz S[6], Heussel CP[7], Silling G[8], Mahne M[2], Franklin J[9], Harnischmacher U[2], Wilkens A[1], Farowski F[1], Karthaus M[10], Lehrnbecher T[11], Ullmann AJ[12], Hallek M[1,3], Groll AH[13]

AAC Accepts, published online ahead of print on 12 September 2011
Antimicrob. Agents Chemother. doi:10.1128/AAC.05134-11

Table 3. Estimated steady state pharmacokinetic plasma pharmacokinetics

	Geometric mean (geometric coefficient of variation)		
Dose (mg QD)	AUC [mg/L*h]	C_{MAX} [mg/L]	C_{MIN} [mg/L]
70	175 (32%)	14.2 (28%)	4.1 (58%)
100	250 (32%)	20.3 (28%)	5.9 (58%)
150	375 (32%)	30.4 (28%)	8.9 (58%)
200	500 (32%)	40.6 (28%)	11.8 (58%)

AUC, area under the concentration-time curve; C_{MAX}, peak, and C_{MIN}, trough plasma concentration.

PK evidence
when DOSE increases
EXPOSURE increases

Cornely OA *AAC* 2011

A Multicenter, Double-Blind Trial of a High-Dose Caspofungin Treatment Regimen versus a Standard Caspofungin Treatment Regimen for Adult Patients with Invasive Candidiasis

Robert F. Betts,[1] Marcio Nucci,[7] Deepak Talwar,[9] Marcelo Gareca,[2] Flavio Queiroz-Telles,[8] Roger J. Bedimo,[5] Raoul Herbrecht,[10] Guillermo Ruiz-Palacios,[11] Jo-Anne H. Young,[4] John W. Baddley,[6] Kim M. Strohmaier,[3] Kimberly A. Tucker,[3] Arlene F. Taylor,[3] and Nicholas A. Kartsonis,[3] for the Caspofungin High-Dose Study Group[a]

High-Dose Caspofungin for Candidiasis • CID 2009:48 (15 June) •

Conclusions. Both caspofungin dosing regimens were effective and well tolerated in patients with invasive candidiasis. No safety concerns were found for caspofungin at a dosage of 150 mg/day.

PV evidence
Still a large Therapeutic Index

Betts RF *CID* 2009

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4880–4887 Vol. 55, No. 10
0066-4804/11/$12.00 doi:10.1128/AAC.00621-11

Pharmacodynamics of Echinocandins against *Candida glabrata*: Requirement for Dosage Escalation To Achieve Maximal Antifungal Activity in Neutropenic Hosts[▽]

Susan J. Howard,[1] Joanne Livermore,[1] Andrew Sharp,[1] Joanne Goodwin,[1] Lea Gregson,[1] A. Alastruey-Izquierdo,[2] D. S. Perlin,[2] Peter A. Warn,[1] and William W. Hope[1]*

School of Translational M... ...enic Health Sciences Centre, Manc... ...nstitute, ...y[2]

Received 4... ...l 23 July 2011

Candida glabrata is a lea... ...dins are increasingly used as first-line agents for the t... ...the optimal regimen for the treatment of invasive *Car*... ...not known. We studied the pharmacokinetics (PK) and pharmacodynamics (PD) of micafungin, anidulafungin, and caspofungin in a

PD evidence?
In Human Clinics?

Caspo experience has confirmed the large therapeutic index

TDM may be useful in selected subset of patients and situations

Howard SJ *AAC* 2011

Clinical factors

– Diarrhea	↑ or (↓)
• Fever	↑
• Ht ?	Whole blood
• Ethnicity	↓ A in black people
• Age	↑ Cl in children
	ageing ↔ except hepatic insufficiency
• Food	concomitant or not, but consistent
• Nyctemer	↑ morning dose (morning TDM)
• Time post Tx	↑ auto inhibition and steroids reduction
• Background	↓ cystic fibrosis
• Liver	↑ C0 due to impaired hepatic function

INTERACTION MEDICAMENTEUSE
classification

a) Préciser	**IMPUTABILITE**	interaction ou	**ETABLIE** **SUSPECTEE**

Niveau de preuve apporté par la documentation scientifique

b) Apprécier	**CARACTERE DE GRAVITE**	**MAJEUR** **MINEUR**

Pertinence clinique

c) Déterminer	**MECANISME**	**PK** **PD**

PK : médiée par variation des concentrations circulantes accessibles à l'adaptation de posologie sans préjuger des effets

INTERACTION MEDICAMENTEUSE : STRATEGIE

*** Interaction authentique à caractère majeur**
→ *action corrective, voire préventive*
PK adaptation dose CyA ; PD modifier choix coprescription

***** Interaction mineure ou simplement suspectée
→ **renforcer la surveillance**

N.B. : 2 interactions modérées de même nature peuvent produire un effet majeur

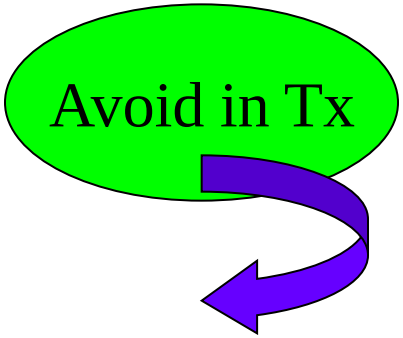
d) Tenir compte des produits modifiant le tractus gastro-intestinal (BD)

e) Penser à renforcer la surveillance si médicament nouveau, surtout s'il présente un fort métabolisme oxydatif.

AF Safety profile

AmphoB

- nephrotoxicity
- tolerance



Echinocandines

+

- hepatic function

Azoles

- LIVER hepatotoxicity

CYP3A4 inhibitors DDI +++

- neurotoxicity (VRZ, ITZ)
- photosensitivation (light protection)
- visual disturbances (VRZ, loading dose)

AZOLES PK

lipidic *(KTZ, ITZ, PSZ)* / hydrosoluble *(FCZ, VRZ)*

LIVER	Metabolism +++	CYP3A4	all <u>but</u> *PSZ*
		DDI	<u>all</u>

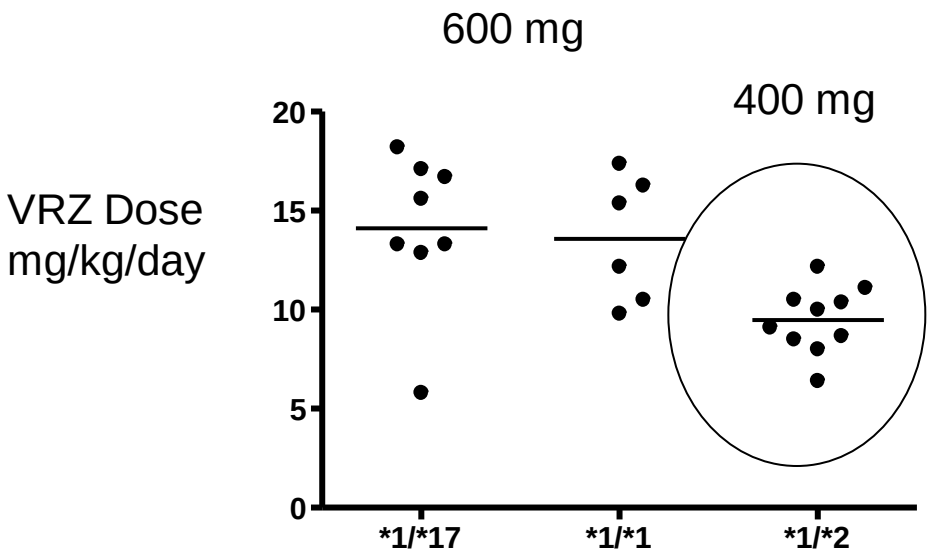
A	pH	*ITZ*
	food	*ITZ, PSZ* (fatty meal) *VRZ* (no food)
E	M, bile	all <u>but</u> *FCZ*
	$t_{1/2}$ long (30h)	all <u>but</u> *VRZ* (6h)

VRZ, non linear PK
PSZ, saturable absorption

PK variability
TDM

long time to SS
loading dose

PGx contribution of CYP2C19 polymorphism in VRZ variability

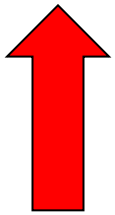


CYP2C19 genotype p<0.01

Cystic fibrosis Lung Tx
[Berge, 2010]

[Ikeda 2004, Weiss 2009]

Drug concentration changes
Consequences



Overdose
Increase <u>both</u> specific toxicities
<u>and</u> therapeutic effect (cf IS)

Overimmunosuppression ,
sustained risk of opportunistic infections

Underexposure
Decrease efficacy
Risk of emergence of resistance (cf AF)

PSZ : interactions (SOT)

n=17

Tacrolimus

The immunosuppressant tacrolimus dose was tapered by a factor **3** during the coprescription with PSZ.

Mean tacrolimus dose was **2.4 ±0.7** mg/day to achieve TRL therapeutic range [5-15] ng/mL.
[Berge, 2009]

n=6

Everolimus

The immunosuppressant everolimus dose was tapered by a factor **2** during the coprescription with PSZ.

Mean everolimus dose was **1.2 ±0.3** mg/day to achieve ERL therapeutic range [4-10] ng/mL.

observations were free from the metabolic inhibition due to CsA on ERL exposure

Calm R, Tx hépatique
VRZ / ERL