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Role of azole concentration monitoring (TDM) in patient management

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4th ADVANCES AGAINST ASPERGILLOSIS
February 4-6, 2010
Rome, Italy
Sheraton Roma

TDM Addressed in 9 questions

Emson 1998

1- Drug's choice appropriate to indication, subpopulation

2- Analytics

3- PK/PD

4- PD response NOT readily assessable

5- PK/PD still apply to specific subpopulation and indication

6- Narrow therapeutic range in the specific context

7- PK parameters unpredictable from variability or cofactors

8- Duration of therapy length regarding benefit from TDM

9- TDM makes a significant difference in the clinical decision-making /clinical judgement alone

TDM

- Analytics

- Narrow therapeutic index — efficacy / safety

- Life-threatening background

- PK variability

- Coprescriptions, DDI

Analytics

Azole :

- plasma (Heparinate Li)

- easily determined using

conventional LC-UV and /or Fluo detection

or LC-MS/MS detection

- after simple deproteinisation

- once at a time or altogether in the same run

X00 mg/day and mg/L range

KKGT (NL)
International proficiency testing Program for Measurement of Azole Antifungal Plasma Concentrations

Radboud University Nijmegen Medical Centre *and*
Nijmegen Institute for Infection, Inflammation and Immunology (N4i)

Available

International

National

- FR (Asqualab)
- UK

KKGT

Association for Quality
Assessment in
TDM and Clinical Toxicology

KKGT

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2009, p. 303–305 Vol. 53, No. 1
0066-4804/09/$08.00+0 doi:10.1128/AAC.00901-08

International Interlaboratory Proficiency Testing Program for Measurement of Azole Antifungal Plasma Concentrations▽

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Received 8 July 2008/Returned for modification 14 August 2008/Accepted 4 November 2008

An international interlaboratory proficiency testing program for the measurement of antifungal drugs was initiated in 2007. This first round was limited to azole antifungals: fluconazole, itraconazole and hydroxyitraconazole, voriconazole, and posaconazole. The results demonstrate the need for and utility of an ongoing proficiency testing program to further improve the analytical methods for routine patient management and clinical research.

TDM

- Analytics
- Narrow therapeutic index — efficacy / safety
- Life-threatening background
- PK variability
- Coprescriptions, DDI

Context IFI

ID **- acquired** **HIV**
- iatrogenic **K, LK drugs**
- therapeutic **IS (SOT, BMT)**
- others **ageing…**

AF objectives **[Aspergillosis]** (Candidosis)
- curative (efficacy)
- prophylaxis, maintenance (safety)

Drugs
- AmphoB, AMBI
- Azoles KTZ**, ITZ, VRZ, PSZ,** FCZ
- Echinocandines (caspofungine)

TDM

- Analytics

→ - Narrow therapeutic index — efficacy / safety

- Life-threatening background

- PK variability

- Coprescriptions, DDI

AF – Therapeutic classes

POLYENES amphotericine B

ECHINOCANDINES -fungine

IV

Increased prophylaxis, need for oral drugs

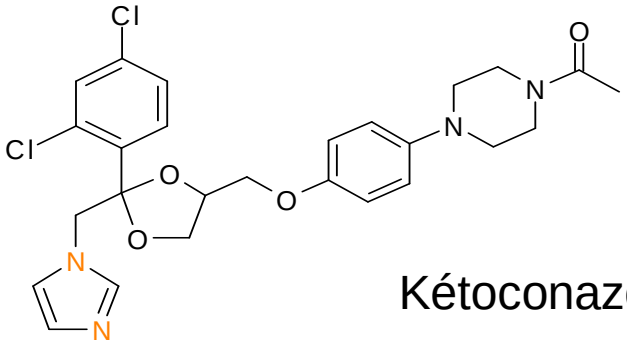
AZOLES –conazole

ITZ itraconazole
VRZ voriconazole
PSZ posaconazole

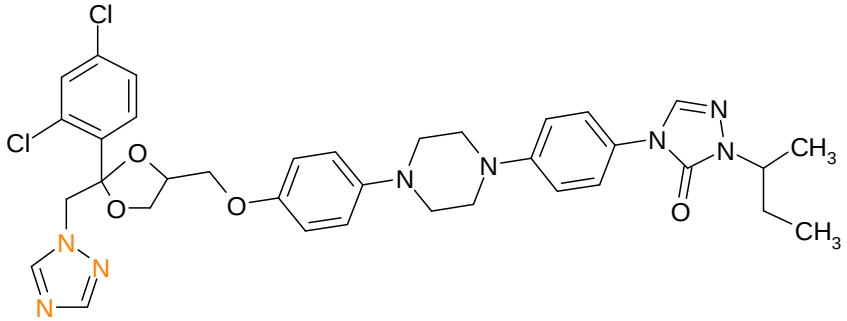
[FCZ] fluconazole

PO ± IV

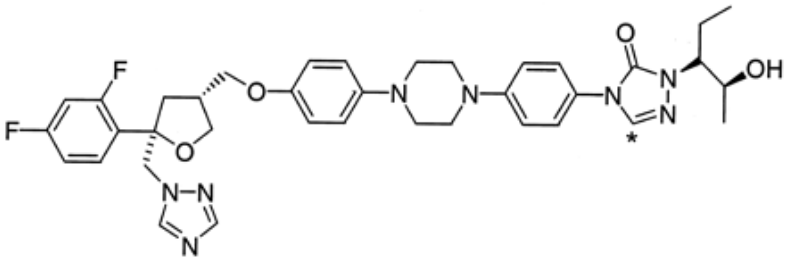
AZOLES



Kétoconazole KTZ NIZORAL®
1981

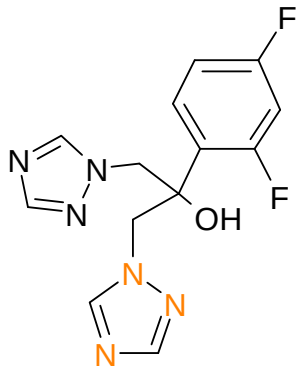


Itraconazole ITZ SPORANOX®
1992

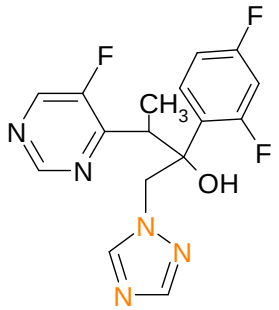


Posaconazole (SCH 56592)

Posaconazole PCZ NOXAFIL®
2005



Fluconazole FCZ TRIFLUCAN®
1990



Voriconazole VRZ VFEND®
2002

Ravuconazole
Phase III

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

AF concentration targets

trough levels (C0)

EFFICACY concerns

Considering PK as a prerequisite to PD

1- detectable level **> 0.2 mg/L**

2- in vitro *Aspergillus ssp* MIC **> 0.5 mg/L** [Trifillio 2005]

3- therapeutic levels > pivotal sudies

*** ITZ +OH-ITZ** **1-2 mg/L**

*** VRZ** **0.5- 2 mg/L** [Purkins, 2002]

> 2 mg/L [Smith, 2006]

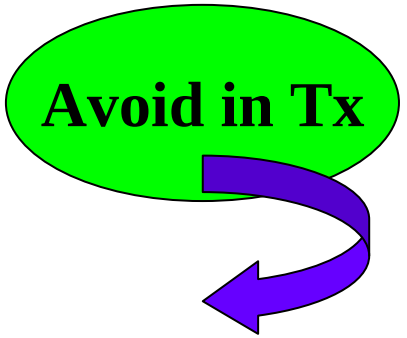
*** PSZ 1 mg/L range seems acceptable from clinical trials**

C0 0.5 –2.5 mg/L range

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)

AF concentration targets

SAFETY concerns : ADR

Not that narrow therapeutic index as IS

Limitations mainly due to **VRZ**

* ITZ	4-5 mg/L	possible
* VRZ	< 4 mg/L	hepatotoxicity [Pascual, 2007]
	2.5 mg/L	neuropathy (CFLTx) [Boussaud, 2008]
	No obvious evidence that higher concentration are useful	
* PSZ	?	Safety OK
		but difficult to achieve high levels

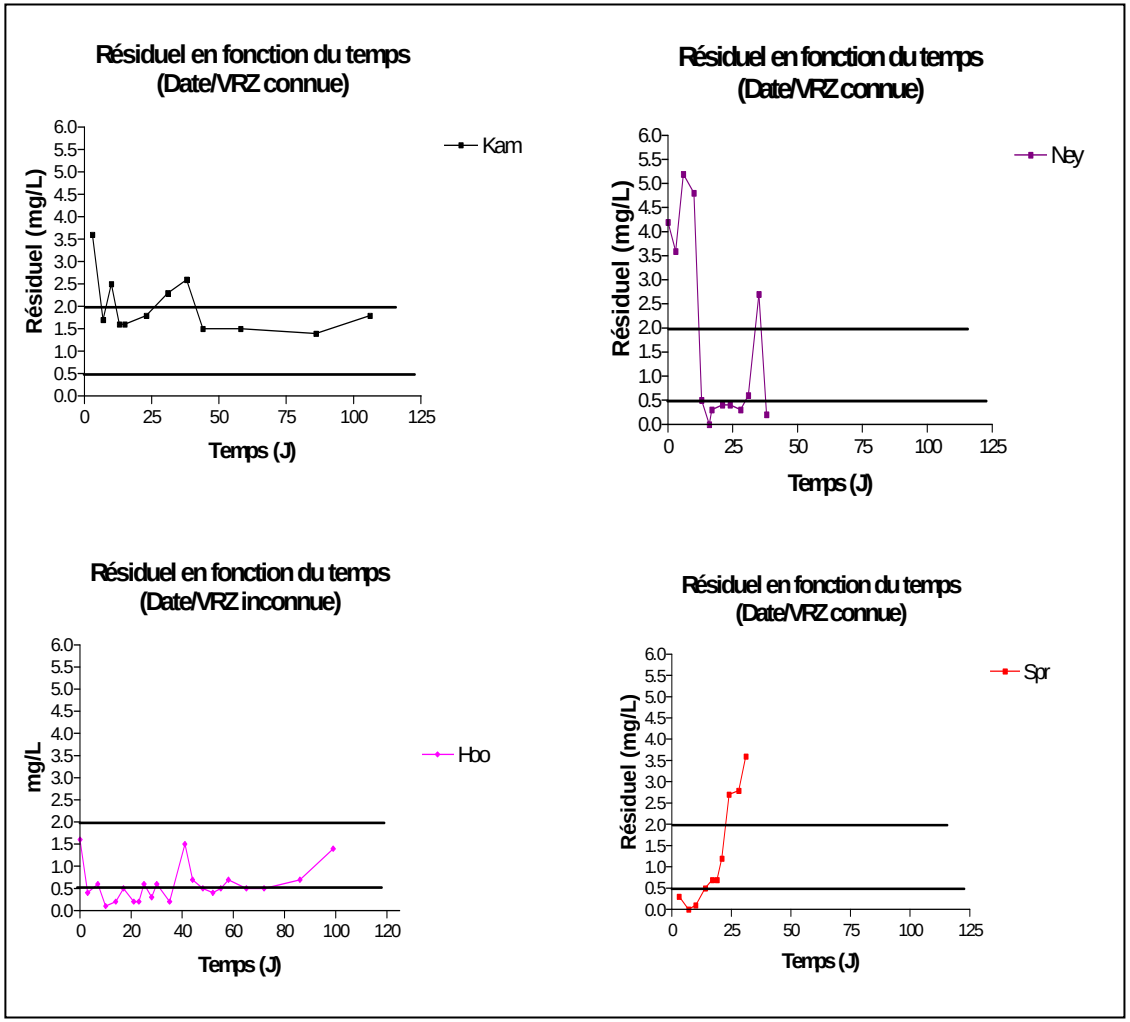
C0 2 – 4 mg/L

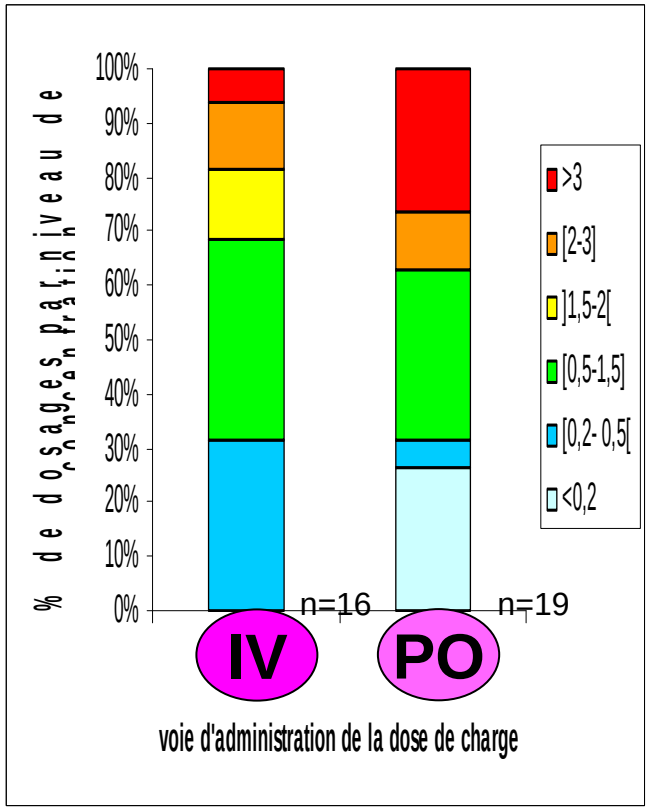
TDM

- Analytics
- Narrow therapeutic index — efficacy / safety
- Life-threatening background
- PK variability
- Coprescriptions, DDI

PK variability in CF

Individual VRZ concentrations profiles



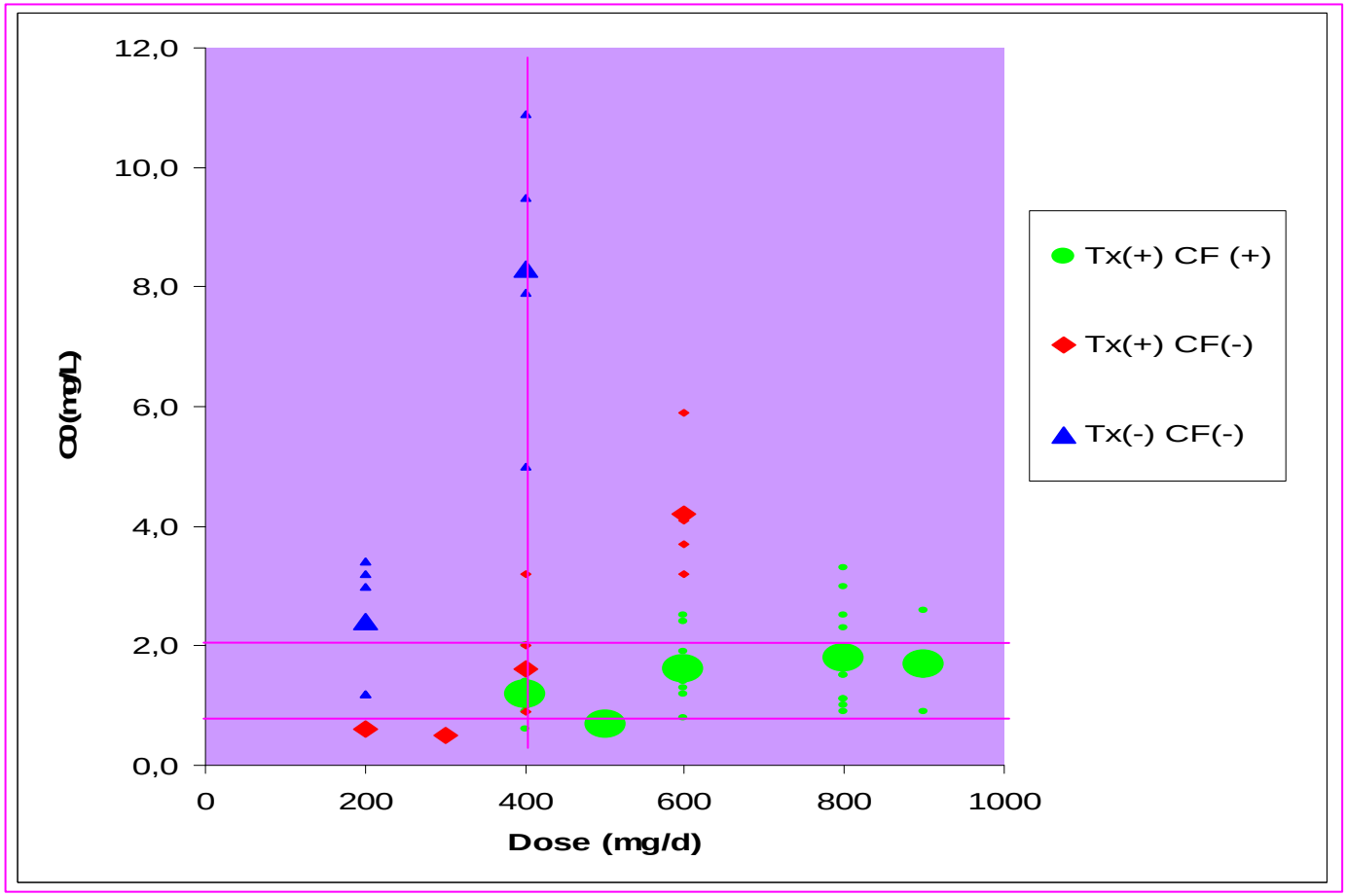


Underdose,even IV

[Berge, 2009]

VRZ trough concentrations upon dose and background

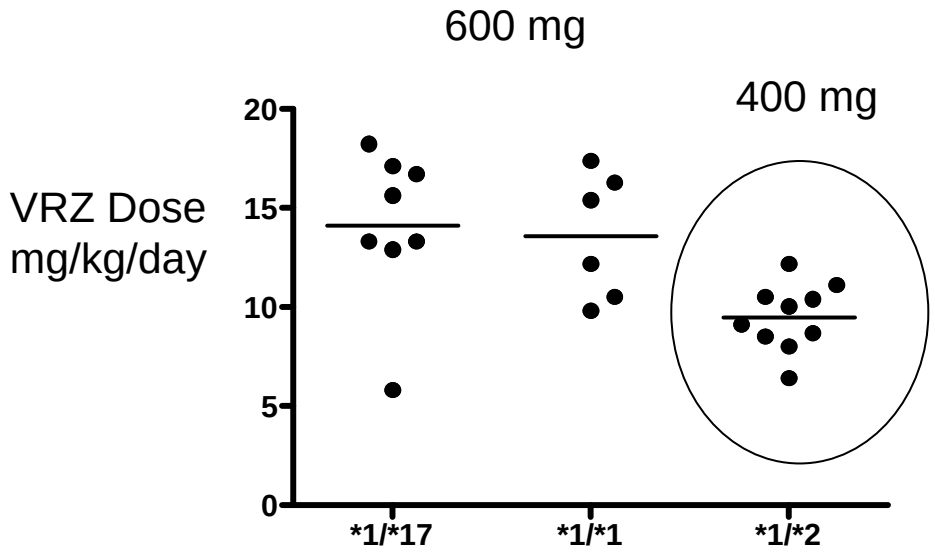
[Imhof 2006, Pascual 2008, Berge, 2009]



The dose regimen necessary to achieve therapeutic VRZ levels in CF Tx (●) was as an average higher and more variable as compared to non CF transplanted patients (◆) or non transplanted patients (♦).

Adaptations conducted up to 800 mg/day appeared to be necessary to reach detectable levels.

PGx contribution of CYP2C19 polymorphism in VRZ variability



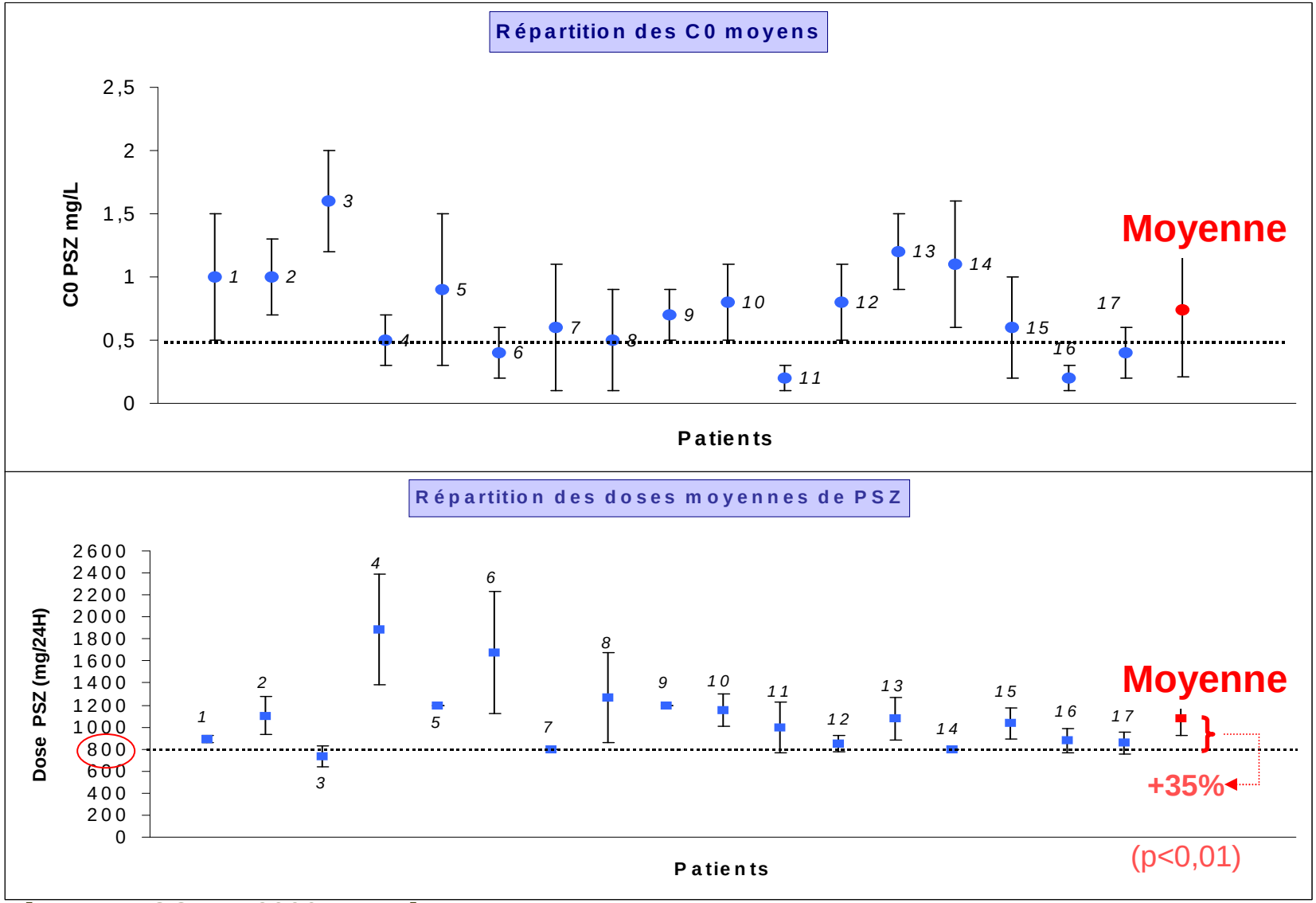
CYP2C19 genotype p<0.01

Cystic fibrosis Lung Tx
[Berge, 2010, submitted]

[Ikeda 2004, Weiss 2009]

PSZ

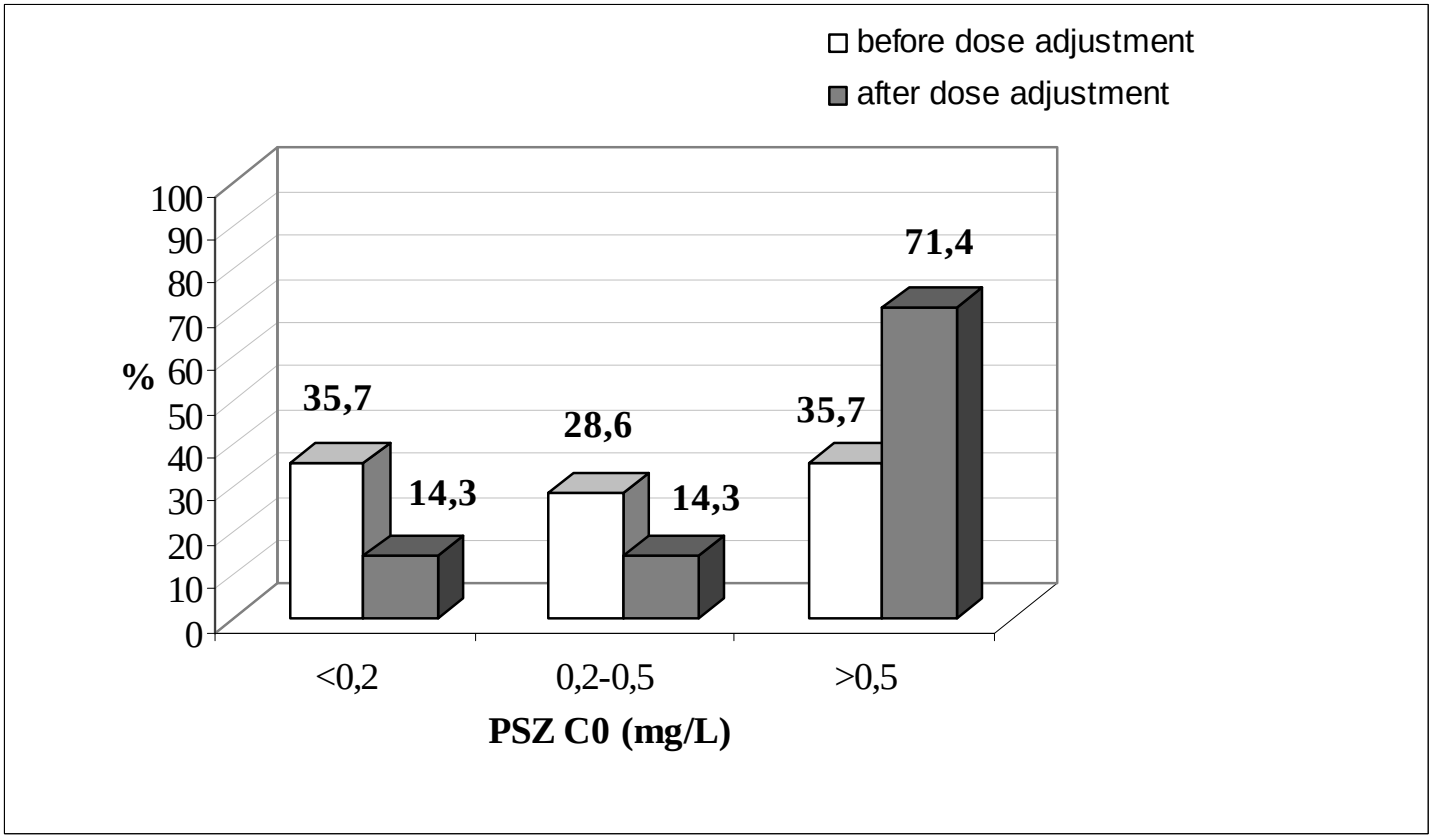
C0 = 0,7 ± 0,5 mg/L **range [0,2-1,6] mg/L**	**Dose = 1085 ± 310 mg/24h** **range [735-1890] mg/24h**



[Berge, ECCMID 2009 #1751]

PSZ Dose adjustment

Dose adjustment was required in 65% of cases (n=10) at 11 ± 3 days



Haematology

	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**

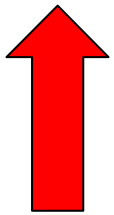
	PSZ LK/BMTx	
	EP	LP
n	13	9
Dose	600	600
C0 ± SD	**0,54 ± 0,36**	**0,55 ± 0,51**

	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)

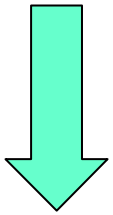
[Lebeaux, 2009] **low and variable PSZ exposure /pediatrics, mucositis and diarrhea**

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)

TDM

- Analytics
- Narrow therapeutic index — efficacy / safety
- Life-threatening background
- PK variability
- Coprescriptions, DDI

AF SAFETY concerns : DDI (1)

[Bruggemann 2008]

- As strong inhibitors of CYP3A4-Pgp system

All of them are concerned,

Including PSZ despite a different metabolic pathway

Ex : IS drugs, quantitative aspects [Billaud 2006, Kovarik 2006]

- As targets themselves (ITZ, VRZ) (PSZ?)

Role of steroids

IS drugs

Steroids

CNI	**CsA**	**cyclosporine**	**nephrotoxicity**
	TRL	**tacrolimus**	**neurotoxicity**
mTOR inh	**SRL**	**sirolimus**	**hematoxicity**
	RAD	**everolimus**	**GI**
			hyperlipemia

CYP3A4 DDI +++

DDI Azoles – CNI : upon the inhibitor

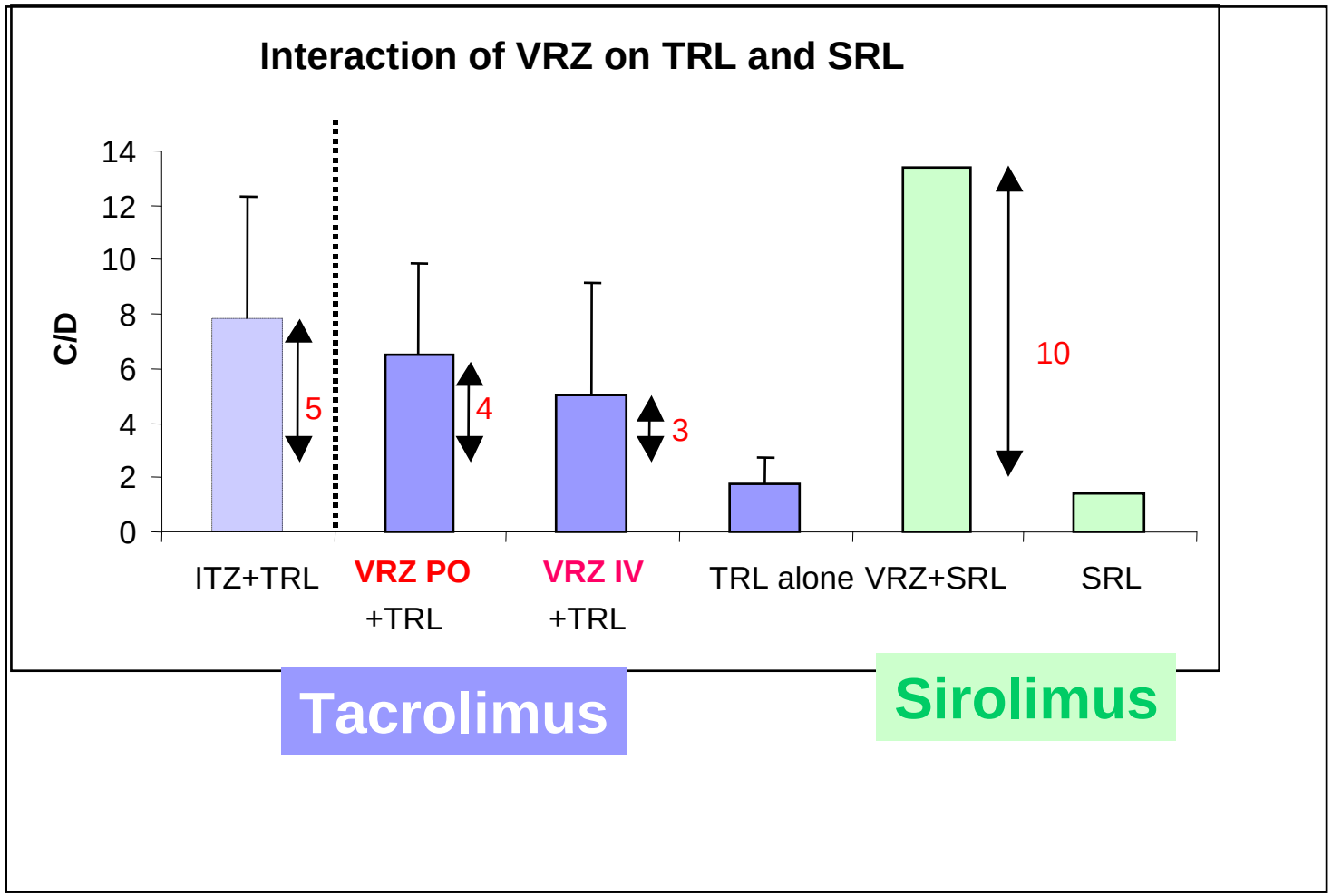
ITZ acts as a stronger inhibitor than VRZ and PSZ regarding calcineurin inhibitors,

C0/D	alone	PSZ+	VRZ+	ITZ+
TRL ($p<0.001$)	1.4 ± 0.6 (n=19)	4.6 ±0.8 (n=12)	5.8 ± 2.6 (n=28)	7.8 ± 4.5 (n=15)

ITZ [Billaud 1998], VRZ [Billaud 2006, Berge 2008], PSZ [Berge 2009]

resulting in a larger dose reduction for tacrolimus (FK) during ITZ as compared with VRZ and PSZ

VRZ : DDI upon the target



PSZ Drug Drug Interaction (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]

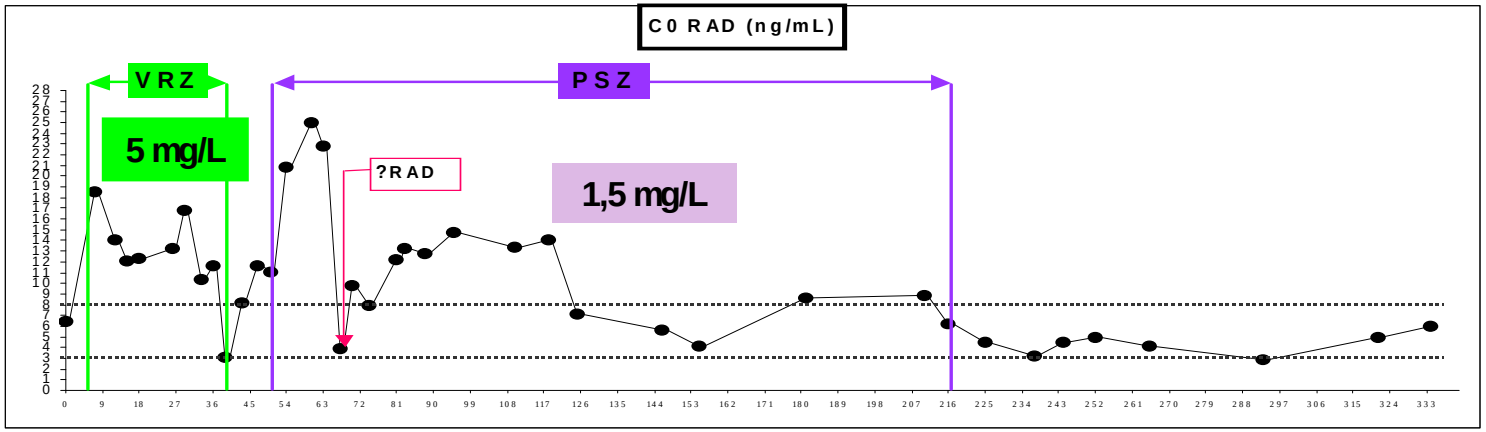
n=6

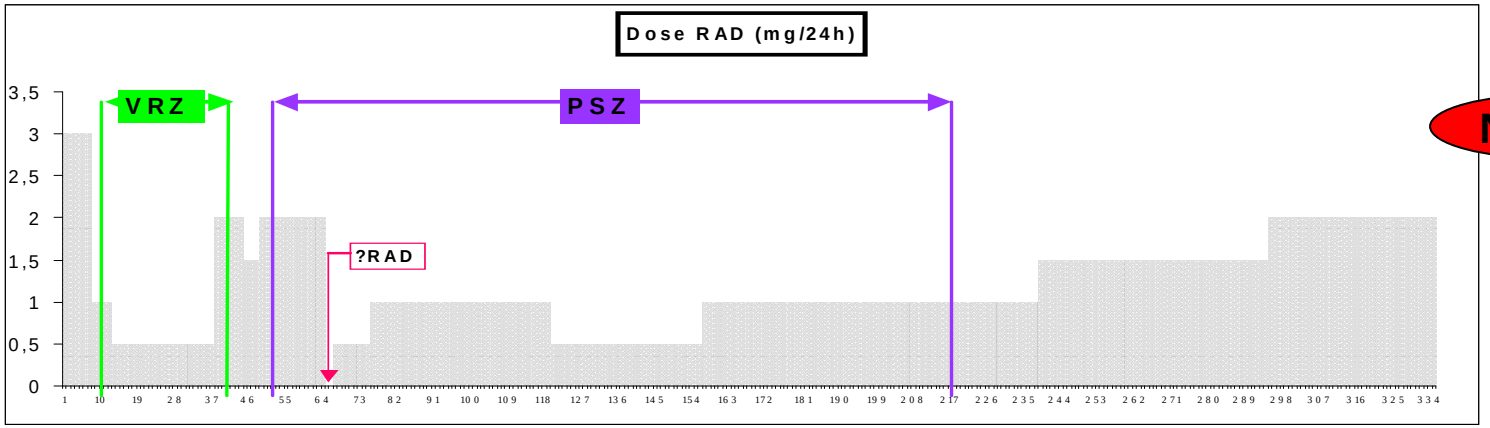
Everolimus

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

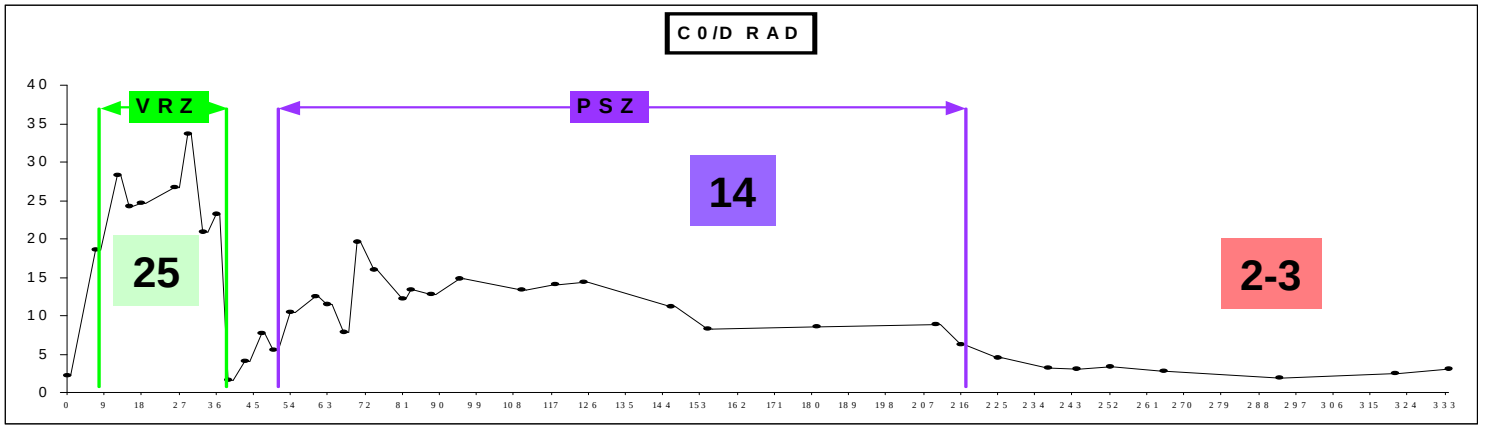
Mean everolimus dose was **1.2 ±0.3** mg/day to achieve ERL therapeutic range [4-10] ng/mL.

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





No CNI



[Billaud CDI 2009]

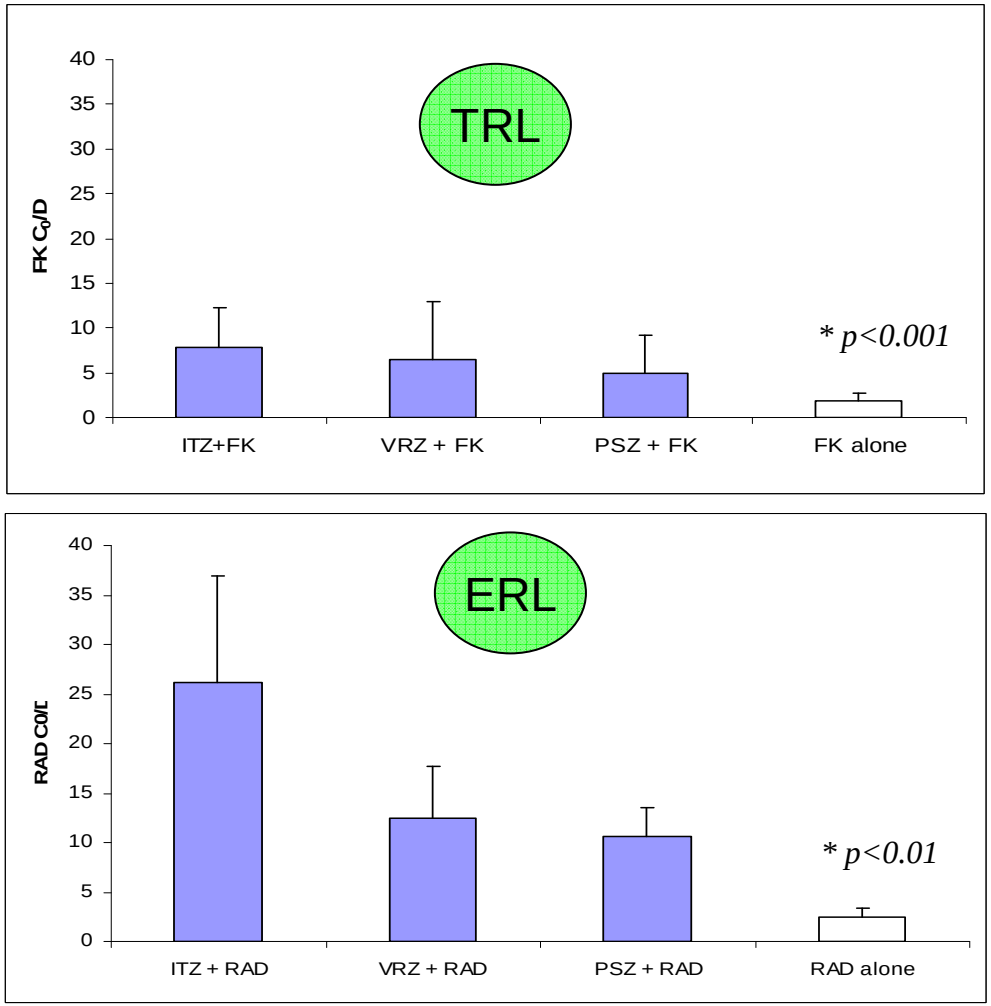
IS Drug Drug Interaction

ITZ > VRZ ~ PSZ — ***Azole-IS DDI***

TRL

PK

ERL



TRL

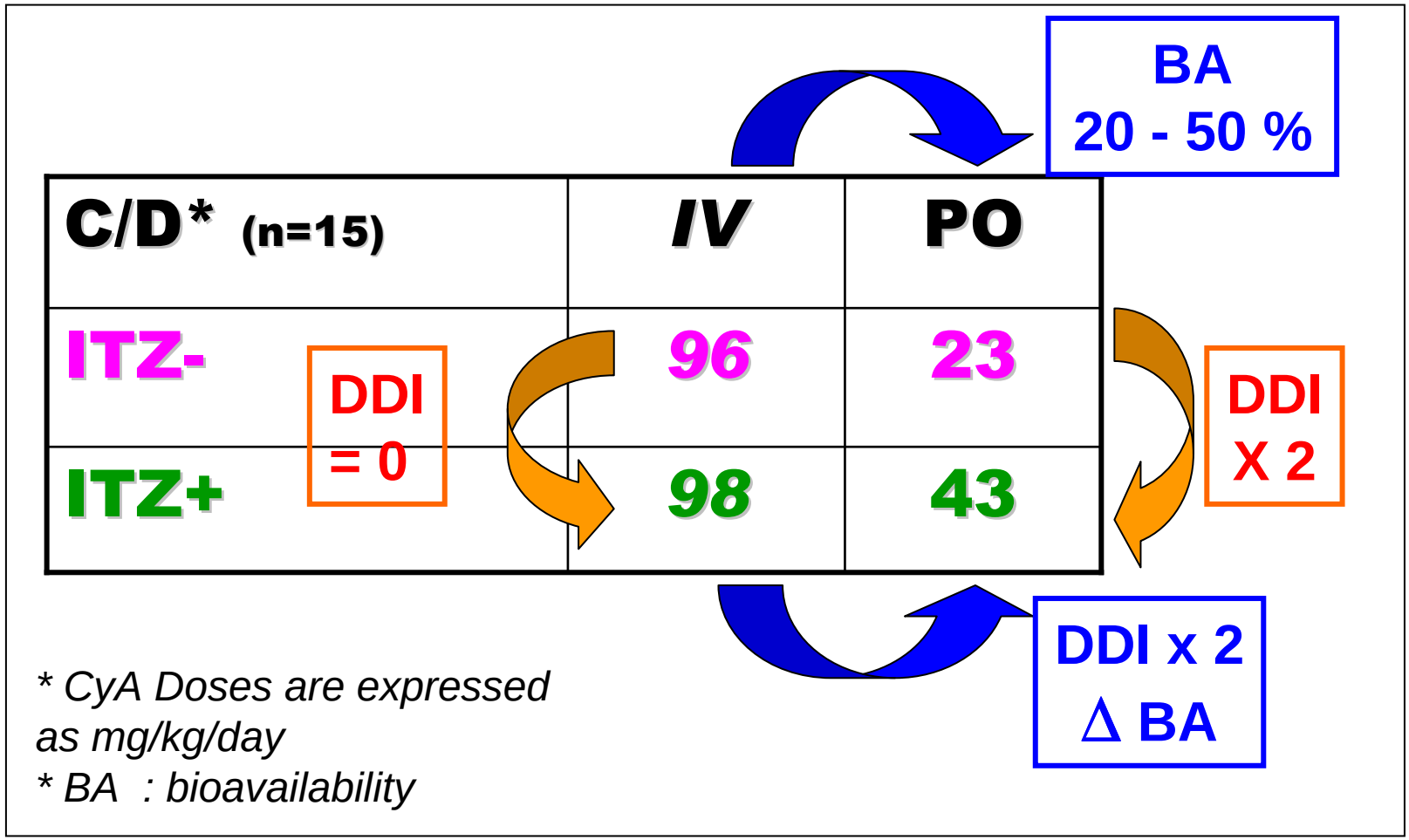
PD

ERL

Clinical consequences

Role of the route of administration
CYP3A4 / Pgp = hepatic + intestinal

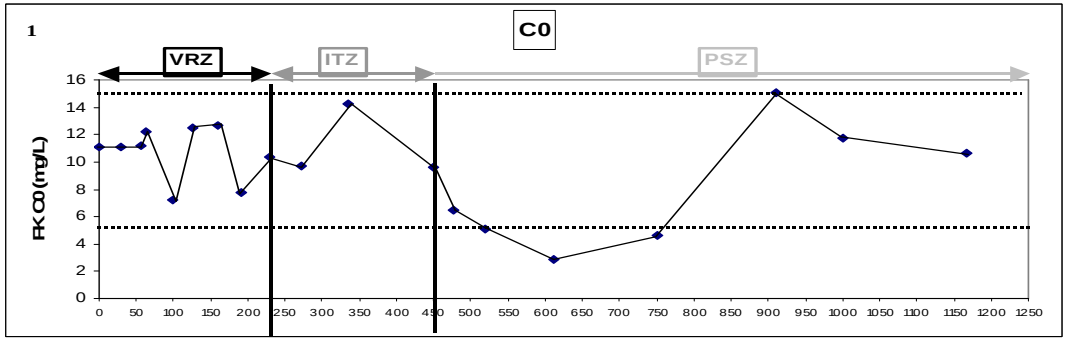
ΔBA + DDI



CyA concentration to dose ratio during ITZ coprescription

Individual TDM basis DDI management : SWITCH and WITHDRAWAL

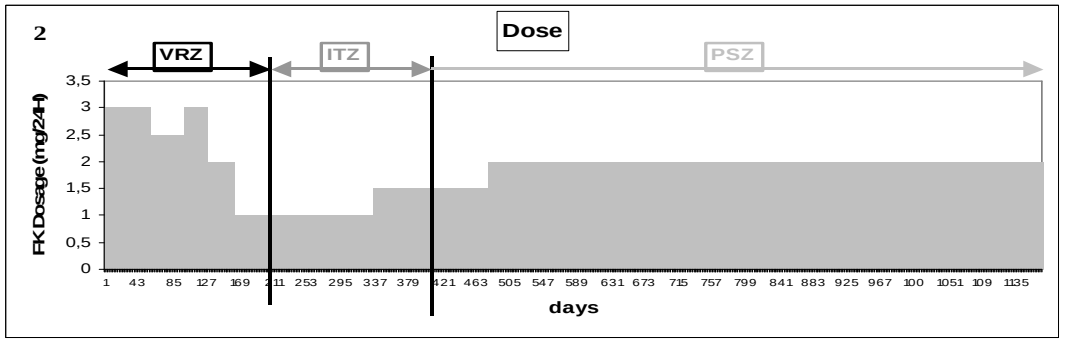
C0



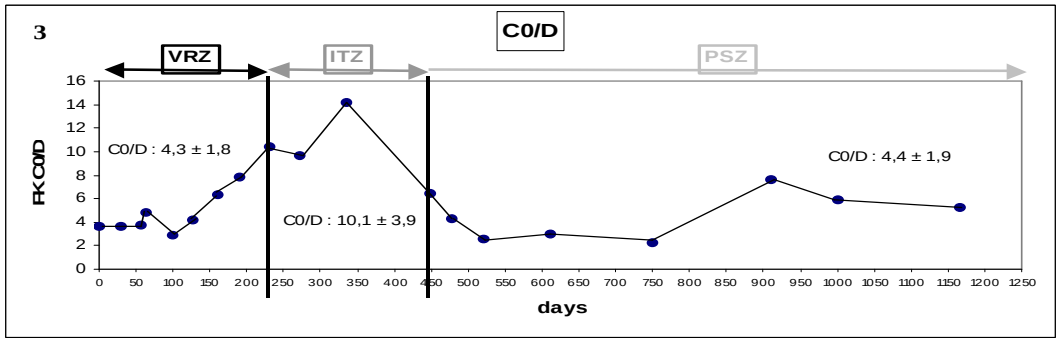
FK Therapeutic drug monitoring in a lung transplant patient with cystic fibrosis during three different consecutive azoles therapy
VRZ then ITZ then PSZ

No dramatic change in FK C0

D



C0/D



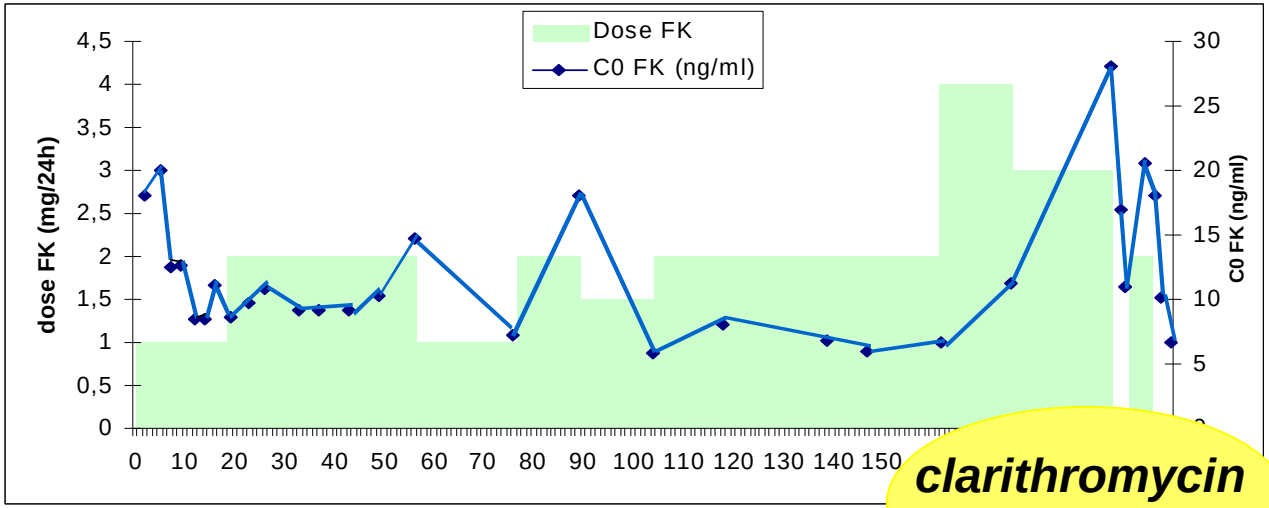
Difference of inhibition on FK metabolism between azoles

ITZ > VRZ ~ PSZ

In case of very high azole concentrations, switch between antifungals must be conducted with caution, specially regarding the use of a loading dose

Interaction VRZ – FK : JOINT TDM

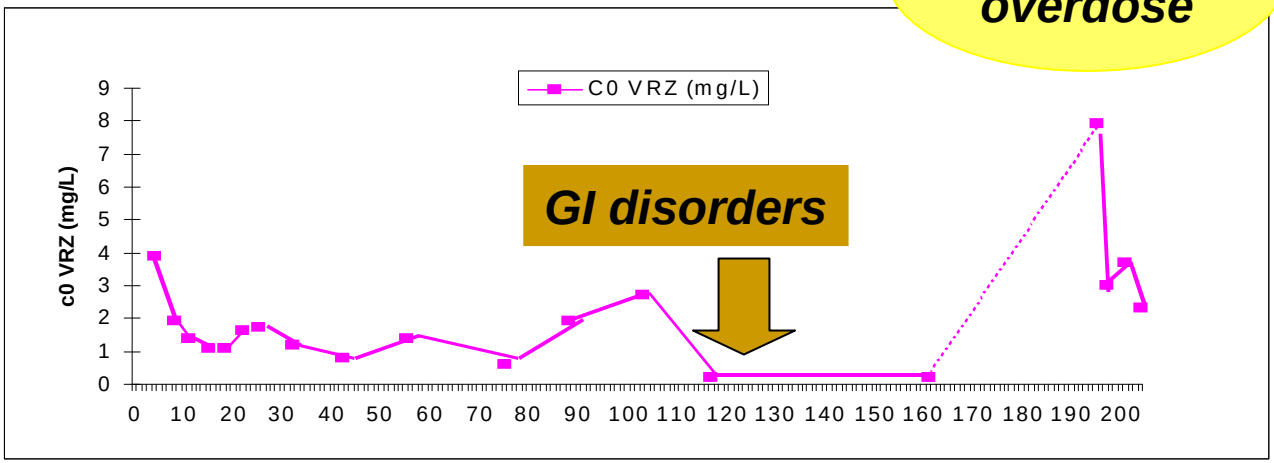
FK



clarithromycin overdose

Dramatic changes in azole concentrations impact the magnitude of the interaction and subsequently the need for adjustment

VRZ



GI disorders

TDM helps in conducting drug withdrawal, reintroduction, when and how much

AF SAFETY concerns : DDI (2)

DDI management

- As inhibitors : quantitative aspects

- As targets : VRZ

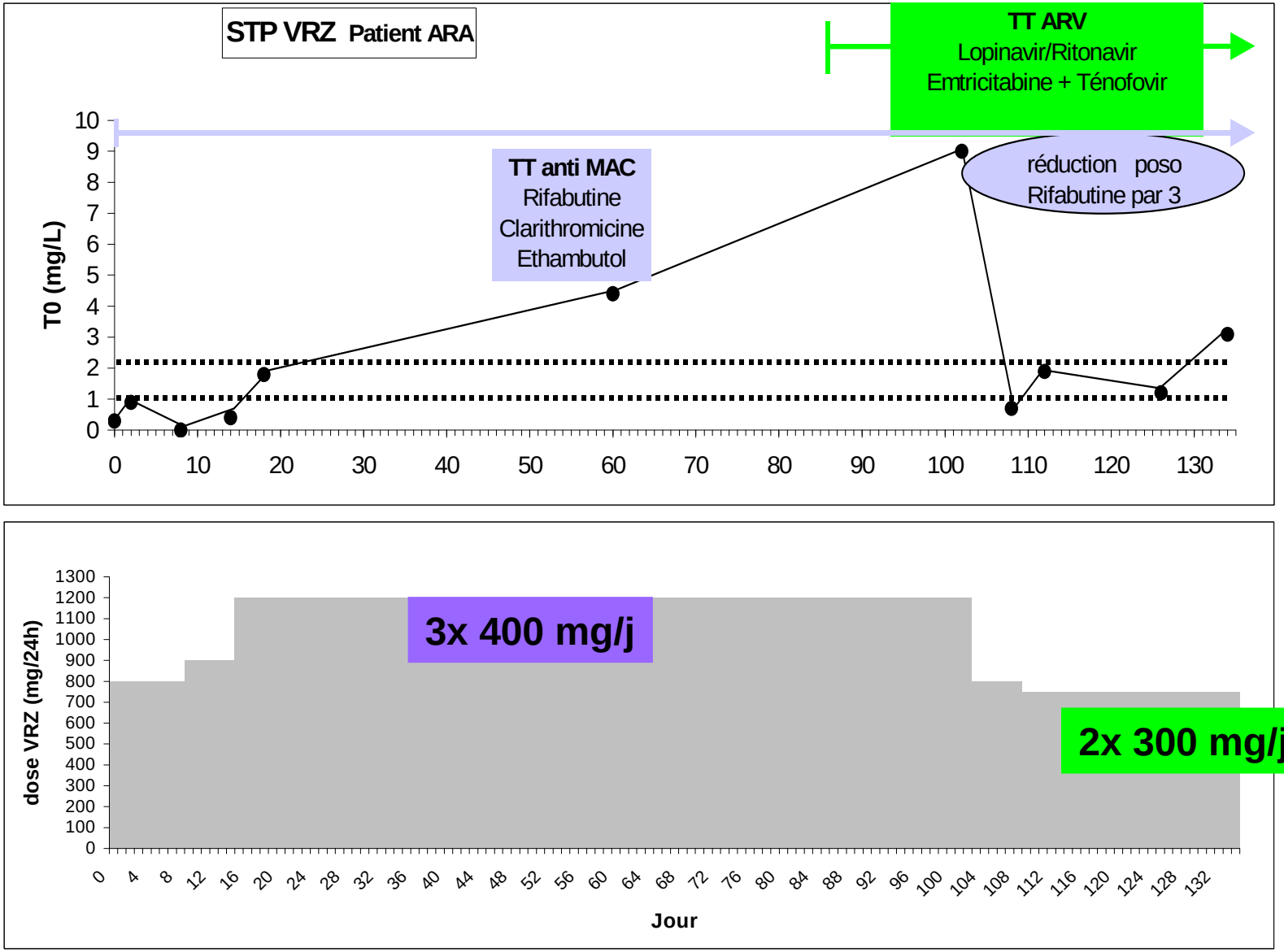
  * *inhibition*

    HIV : protease inhibitors (RTV)

    switch ITZ-VRZ

    steroids

  * *induction* : rifampicin +++



More than 2 drugs influencing CYP3A4 without TDM : FORGET IT

PPI

- **VRZ**

  2C19

  no influence

  [Wood, 2006]

- **PSZ**

  susceptibility to omeprazole

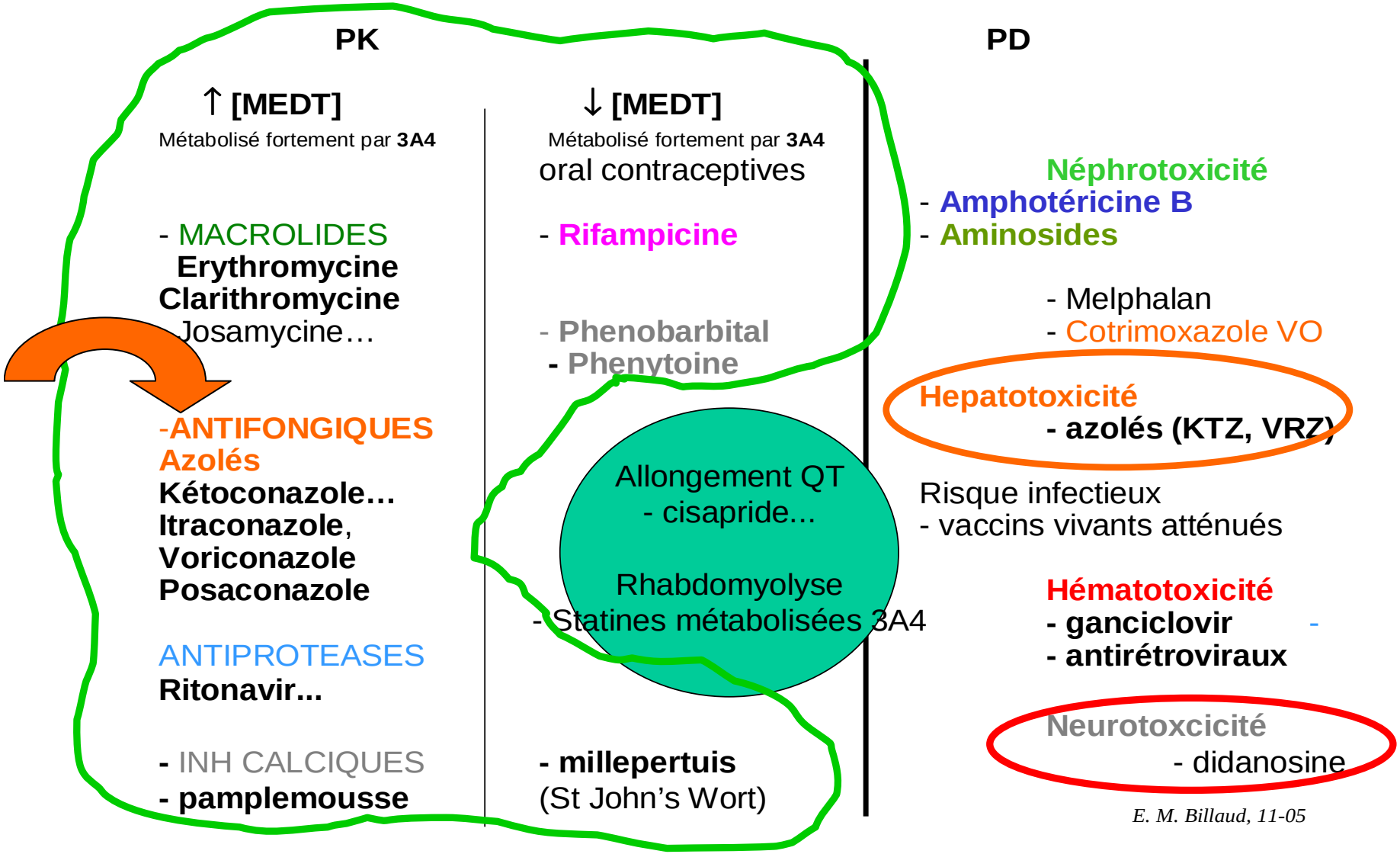
  [Alffenaar, 2009]

Azoles DDI target risks

PD - nephrotox(amphoB), hematotox, hepatotox
- CV (QTc,TSDP, K+)
- neuromuscular

PK A (pH, food)
D
M inhibition or induction CYP3A4 - Pgp +++
Ex U
Bile

Established INTERACTIONS



E. M. Billaud, 11-05

AF combination

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

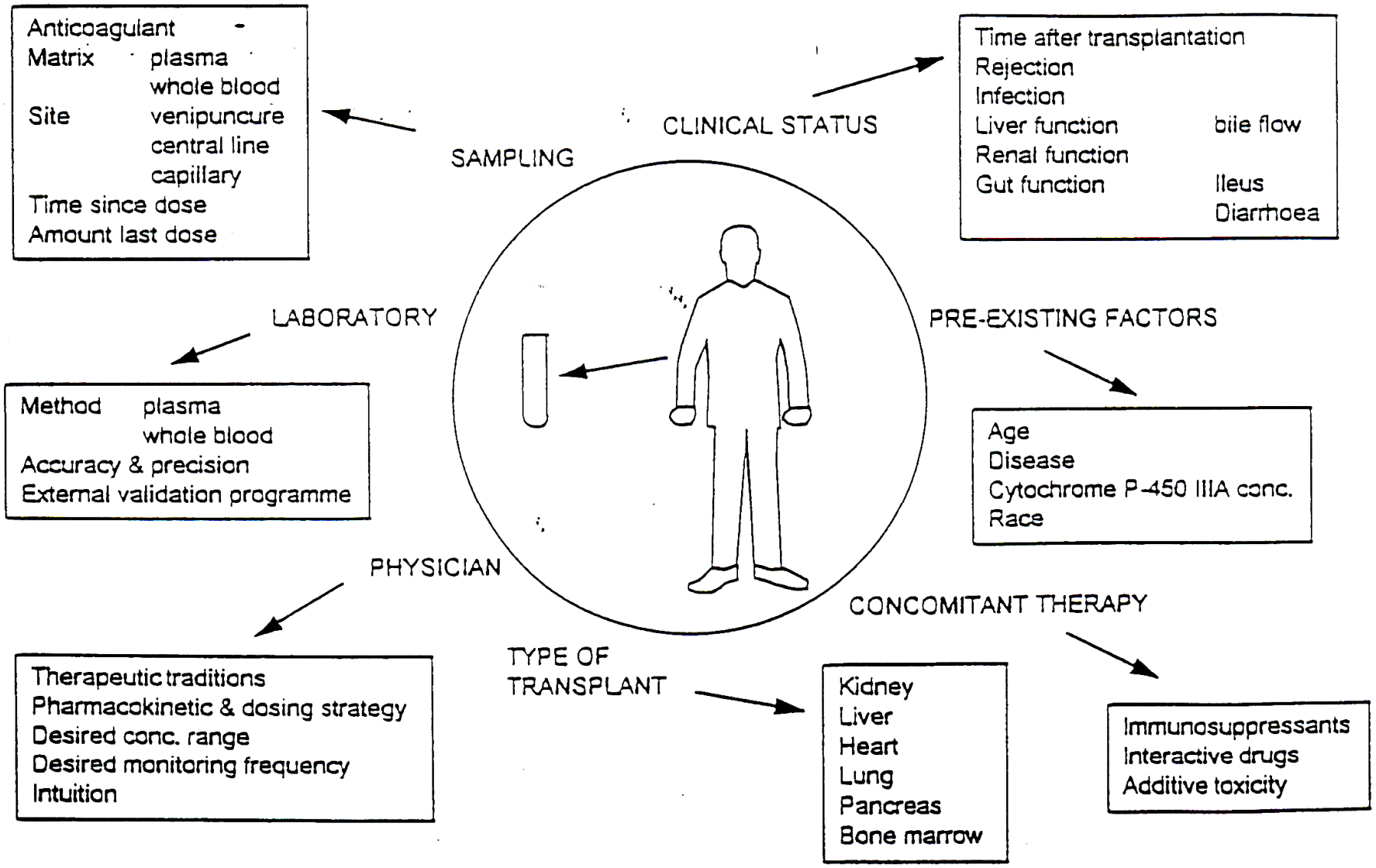


FIG. 1. Some points of consideration when evaluating an immunosuppressive drug sample.

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

PK = N, not S **« pharmacokinetics : required, not enough»**

TDM

TDM is of importance to quantify the relative intensities of interactions in order to support the management of these narrow therapeutic index drugs :

- to attest the obtention of detectable stable azole levels,
regarding both efficacy
and the full appreciation of the interaction

- to pilot the switch between drugs of the same class
(calcineurin inhibitors and/or azoles)

- to manage switch between routes of administration (IV/PO)

- Valuable at the introduction but after withdrawal as well
- Maximal effect at steady-state (respective half-lives related)
- Function of DOSES
- Influenced by inhibitor concentration changes

COST issues

Testing reagents, equipments, technical staff

< 50 € / test

Treatment

> 100 € / day

Inapropriate dose adjustement
Complication,
prolonged hospitalisation, death

[Touw, 2007]

TDM Conclusion (1)

- Analytics : YES — LC, IPTS

- Narrow therapeutic index
  - efficacy : low exposure (inefficacy, R)
  - safety : high exposure (LIVER)
    - VRZ + (hepatotox, neurotox)
    - ITZ +/-
    - PSZ -
  - photosentisation, skin disorders

- Life-threatening background : opportunist IFI

- PK variability : YES (CF, pediatrics, mucositis)

- Coprescriptions, DDI : YES +++

TDM Addressed in 9 questions

Emson 1998

1- Drug's choice appropriate to indication, subpopulation

2- Analytics

3- **PK/PD and PK modelling** [Hope, 2009]

4- PD response NOT readily assessable

5- PK/PD still apply to specific subpopulation and indication

6- Narrow therapeutic range in the specific context

7- PK parameters unpredictable from variability or cofactors

8- Duration of therapy length regarding benefit from TDM

9- TDM makes a significant difference
in the clinical decision-making /clinical judgement alone

TDM Conclusion (2) : proof level

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

But emerging evidence, at least for special populations that fortunately are very representative

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**	

TDM need for <u>collaborative</u> prospective studies…..indeed already useful….YES

A « one patient at a time » management

a multidisciplinary, specialised, collaborative practice

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