Prophylaxie antifongique en hématologie et Suivi Thérapeutique Pharmacologique

D. CAILLOT (Dijon)

C. PADOIN (Bobigny)

ECIL 3 guidelines on antifungals (1/2)

Leukemia patients, induction chemotherapy		
Fluconazole (50–400 mg/day)	CI	Azoles should not be used empirically in case of prevoius azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole oral solution (2.5 mg/kg b.i.d.)	CI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of prior azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole (200 mg t.i.d.)	AI	Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Echinocandins IV	Insufficient data	
Polyenes IV	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***BI***	***The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI***
Allogeneic HSCT recipients, initial neutropenic phase		
Fluconazole (400 mg q.d. i.v. or oral)	AI	Azoles should not be used empirically in case of previous azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole	No data	
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending the publication of the full paper***
Micafungin (50 mg q.d. i.v.)	CI	
Polyenes i.v.	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***BII***	***The ECIL recommendation for aerosolized ampho B deoxycholate is DI***

Maertens et al, Bone Marrow Transplantation , 2011

ECIL 3 guidelines on antifungals (2/2)

Allogeneic HSCT recipients, GVHD phase		
Fluconazole (400 mg q.d. i.v. or oral)	CI	Azoles should not be used empirically in case of previous azole prophylaxis
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of prior azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole	AI	Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending the publication of the full paper***
Echinocandins i.v.	Insufficient data	
Polyenes i.v.	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***Insufficient data***	

Maertens et al, Bone Marrow Transplantation , 2011

Les antifongiques azolés utilisés en prophylaxie en hématologie

- **Fluconazole**
- **Itraconazole**
- **Posaconazole**
- **Voriconazole**

- des spectres d'activités différents
- des caractéristiques physico-chimiques différentes
- des caractéristiques pharmacocinétiques différentes
- des positionnements différents
  (prophylaxie primaires ou secondaires)

Actuellement vous recommandez / réalisez un STP pour :

A – Fluconazole, Itraconazole, Voriconazole, Posaconazole

B – Itraconazole, Voriconazole, Posaconazole

C – Voriconazole, Posaconazole

D - Voriconazole

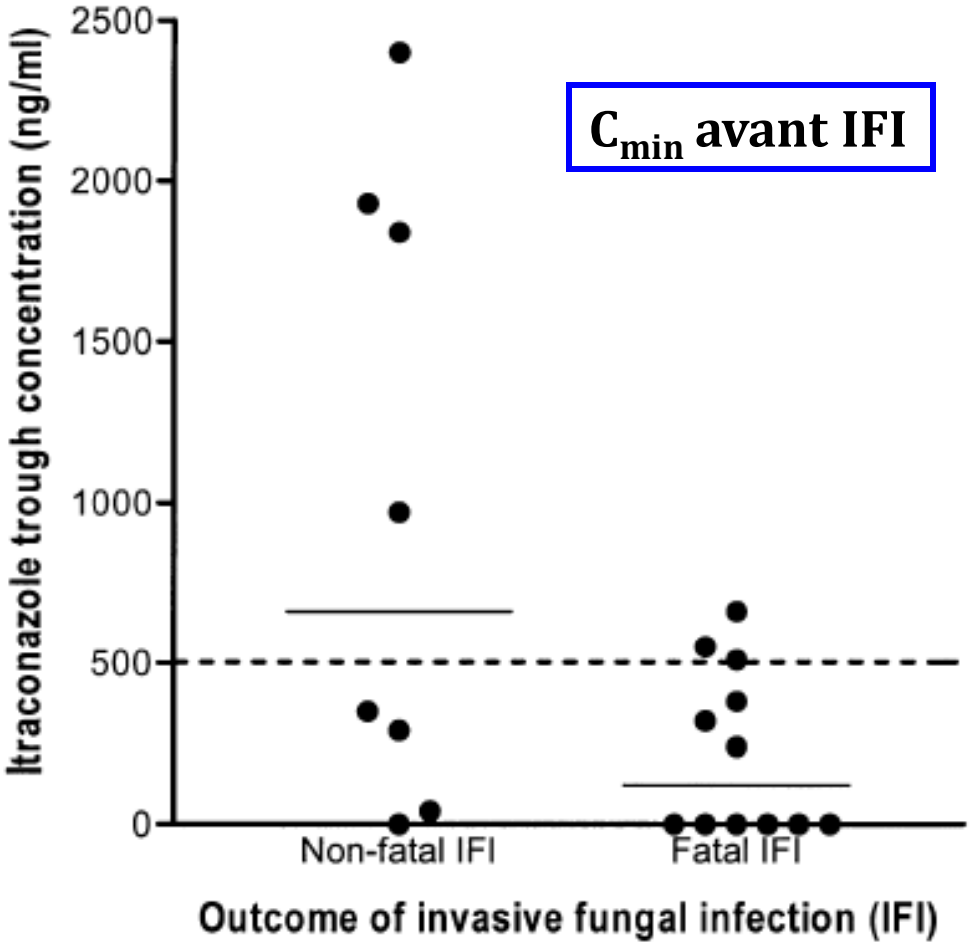
Prophylaxie
et
relation concentration / efficacité
des antifongiques azolés

Itraconazole : prophylaxie chez le patient neutropénique

n=150 (62% LAM, 15% LAL)

287 épisodes de neutropénie entre 1994 et 1998

20 IFI



C_{min} avant IFI

Glasmacher, Mycoses, 1999

Posaconazole en prophylaxie chez des receveurs allogéniques de HSCT présentant une GVH

n = 246

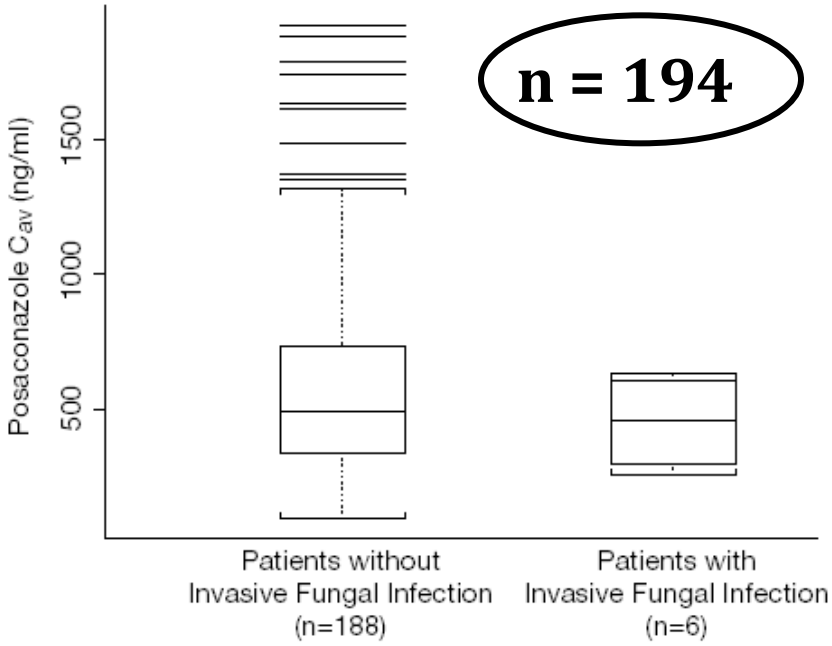
GVHD aiguë (n=162, 66%) → **4 IFI**

GVHD chronique (n=83, 33%) → **1 IFI**

5 IFI	**241 non IFI**
C_{av}= 611 ng/mL	C_{av}= 922 ng/mL
669+/-543 ng/mL	1131+/-759 ng/mL
[158-1562 ng/mL]	[0-3650 ng/mL]

Krishna, Pharmacotherapy, 2007

Posaconazole en prophylaxie chez des patients neutropéniques (LAM ou SMD)



Pas de différence :
Pb de l'incidence des IFI

Covariate	p Value[b] C_{av}	p Value[b] C_{max}
Patient characteristics		
Age	0.4637	0.3796
Sex	0.3242	0.2733
Race, ethnicity[c]	0.0028	0.0021
Baseline body weight	0.1716	0.1711
Baseline body surface area	0.1157	0.1075
Variables at baseline (on or before day 7)		
γ-Glutamyl transferase level	0.0184	0.0353
Liver enzyme levels	0.4077	0.2993
Mucositis	0.6409	0.7311
Neutropenia	0.4575	0.4532
Diarrhea	<0.0001	<0.0001
Vomiting	0.5561	0.6718
H_2 receptor antagonist use	0.5887	0.4758
Proton pump inhibitor use	0.0010	0.0004

-47%

-26%

Etude : standardisation de la prise alimentaire

Krishna, Pharmacotherapy, 2008

Two Year Experience of Posaconazole (POS) Prophylaxis during the First 100 Days in Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Recipients

W. KLAAS[1], A. I. K. KARSTEN[1], R. KRÜGER[2], K. KOLBE[1], R. G. MEYER[1]
W. HERR[1], M. THEOBALD[1], A. J. ULLMANN[1*]

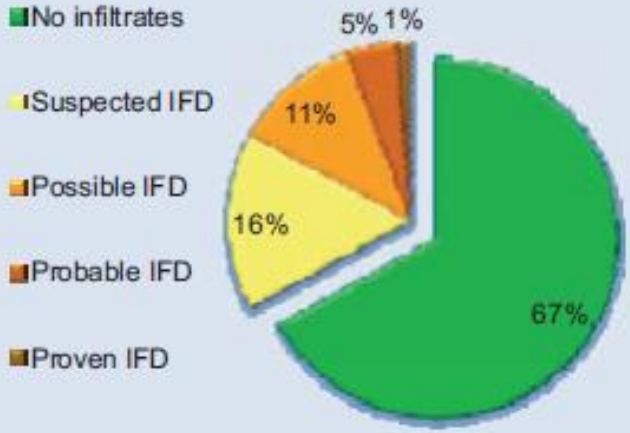
As per institution recommendation, patients were supposed to receive up to 70 days antifungal prophylaxis after allogeneic HSCT. Antifungal agent of choice is posaconazole 200 mg t.i.d.. If the patient is unable to eat, the dosage was increased to 200 mg q.i.d.. Unless the patient developed moderate to severe GVHD requiring an additional immunosuppressive agent, the patient stopped antifungal prophylaxis at day +70.

Patients	N=90	age mean (range)
Female	32	45.8 (18-67)
Male	58	46.4 (22-68)

Diseases (1)	patients
AML	42
ALL	10
MDS	7
SAA	6
NHL	4
Multiple myeloma	4
CML	3

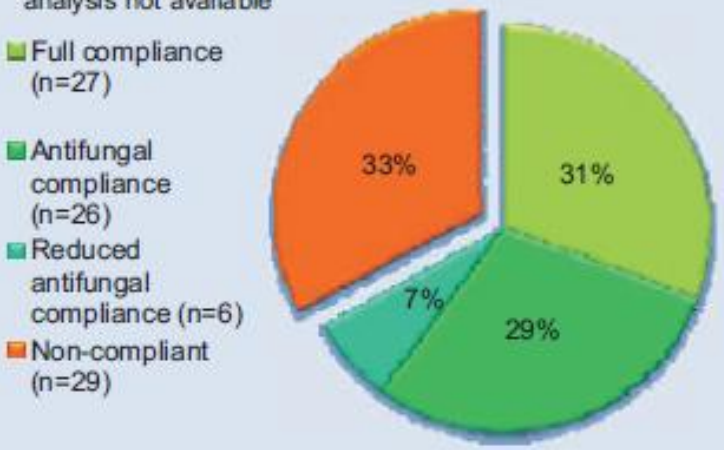
Diseases (2)	patients
CMML	3
OMF	3
ZNS NHL	3
Other	3
Hodgkin's Disease	2
AILD	1
CLL	1

OUTCOME:



Compliance

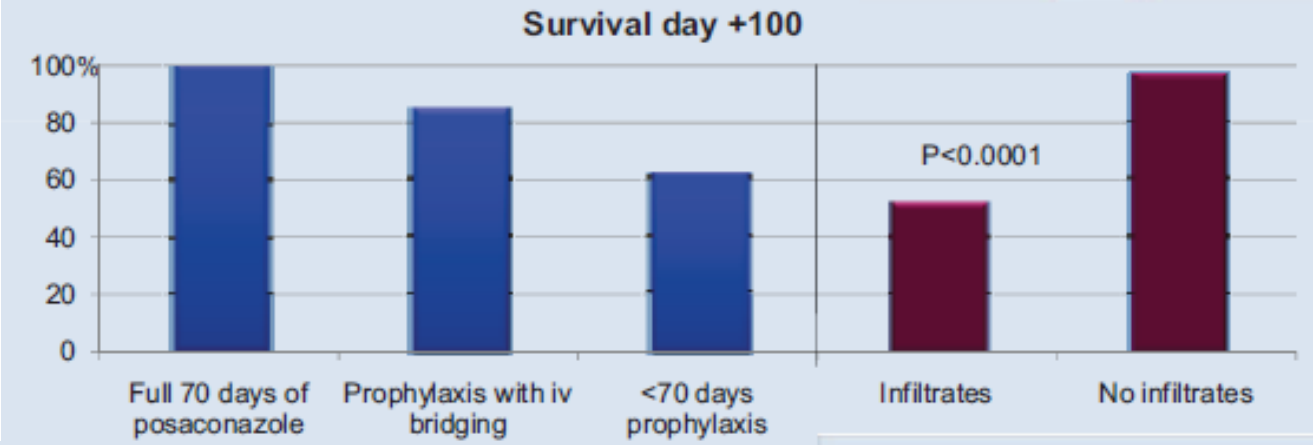
In 2 patients information on antifungal prophylaxis was at analysis not available

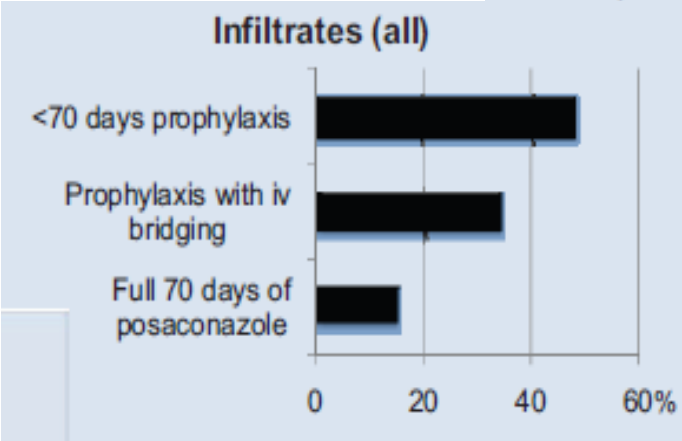


Two Year Experience of Posaconazole (POS) Prophylaxis during the First 100 Days in Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Recipients

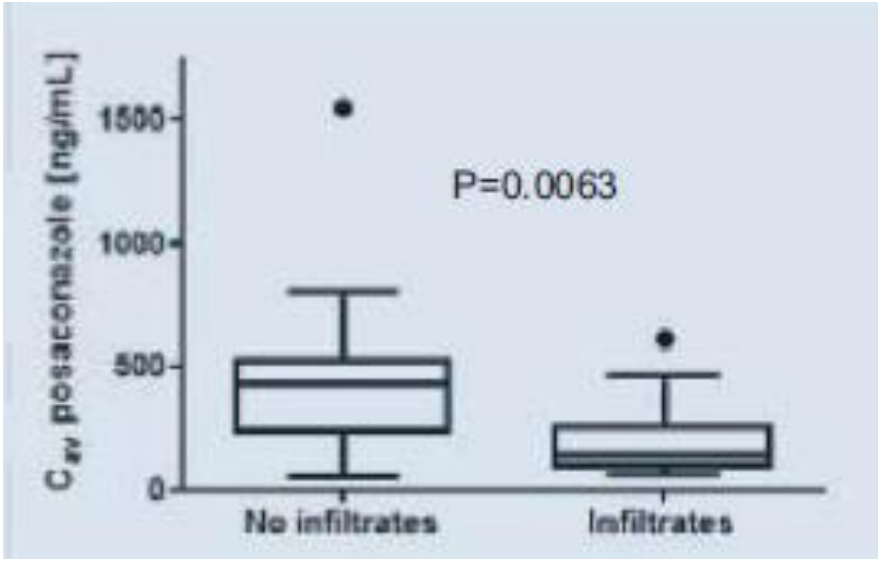
W. KLAAS[1], A. I. K. KARSTEN[1], R. KRÜGER[2], K. KOLBE[1], R. G. MEYER[1]
W. HERR[1], M. THEOBALD[1], A. J. ULLMANN[1*]

50 YEARS ICAAC





70 days vs < 70days	N(%) n=59	N(%) n=29	p-value
No infiltrates	44 (74.6%)	15 (51.7%)	0,0321
Poss & prob & proven IFD	8 (13.6%)	7 (24.1%)	0,22
Death	5 (8.5%)	11 (37.9%)	0,0008

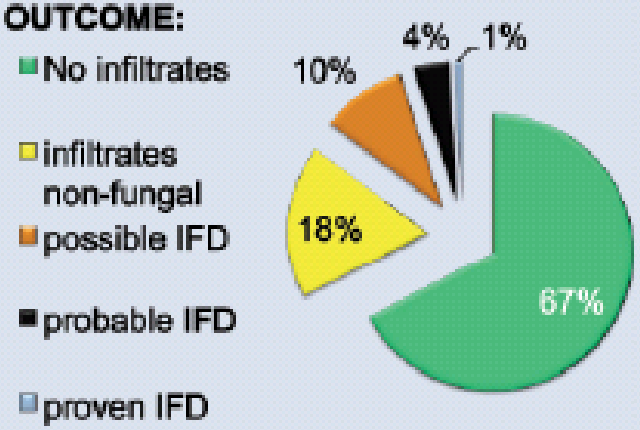


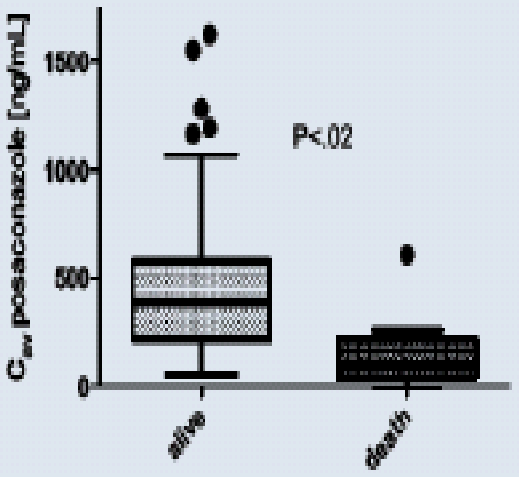
Early Posaconazole (POS) Prophylaxis during the First 100 Days in Allogeneic Hematopoietic Cell Transplant (HCT) Recipients. A Single Center Experience

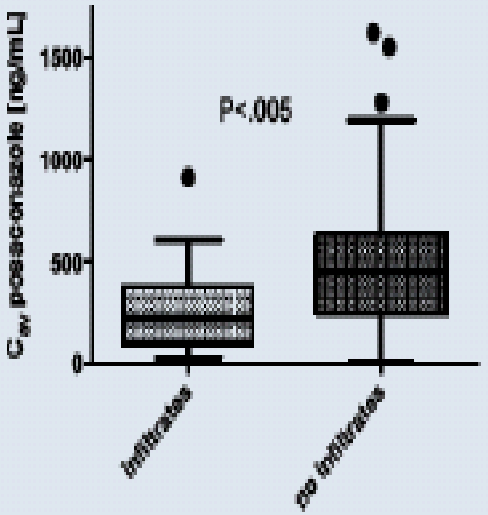
W. KLAAS[1], A. I. K. KARSTEN[1], K. KOLBE[1], R. KRÜGER[2], R. G. MEYER[1]
W. HERR[1], M. THEOBALD[1], A. J. ULLMANN[1*]

CHICAACGO
51st ICAAC ~ SEPT. 17-20, 2011 ~ CHICAGO

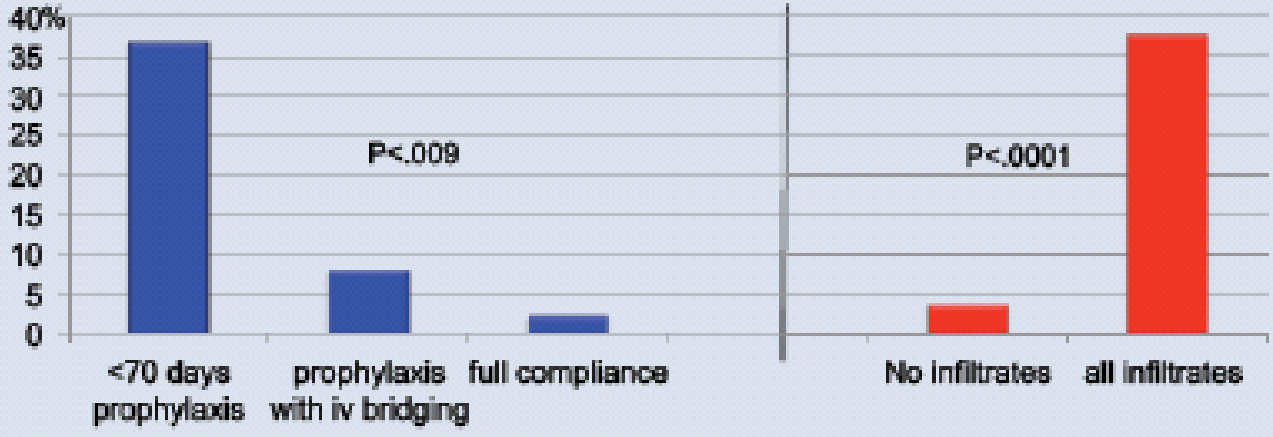
OUTCOME:







MORTALITY:



Diseases (1)	patients
AML	58
ALL	18
MDS	9
SAA	7

Clinical Utility of Posaconazole Therapeutic Drug Monitoring

Michael Dolton[1,2], John Ray[3], Sharon Chen[4], Kingsley Ng[4], Deborah Marriott[3], Andrew McLachlan[1,2]

CHICAACGO
51st ICAAC ~ SEPT. 17-20, 2011 ~ CHICAGO

- 85 patients received posaconazole during the study period, with 538 concentrations measured.
- Posaconazole concentrations were found to be frequently low in most patients (median 467 ng/mL (range 0 – 4564 ng/mL).

Table 1 – Prophylaxis failure stratified by posaconazole concentration

Quartile	Posaconazole concentration (mg/L)*	Prophylaxis failure
1st	0 – 314.75 (196.5)	39% (7/18)
2nd	315 – 444.5 (374)	17% (3/18)
3rd	445 – 734 (533.5)	11% (2/18)
4th	735 – 2035 (1173)	0% (0/18)

*Quartile range (quartile median)

Figure 1 – Model predicted probability of prophylaxis failure according to posaconazole concentration

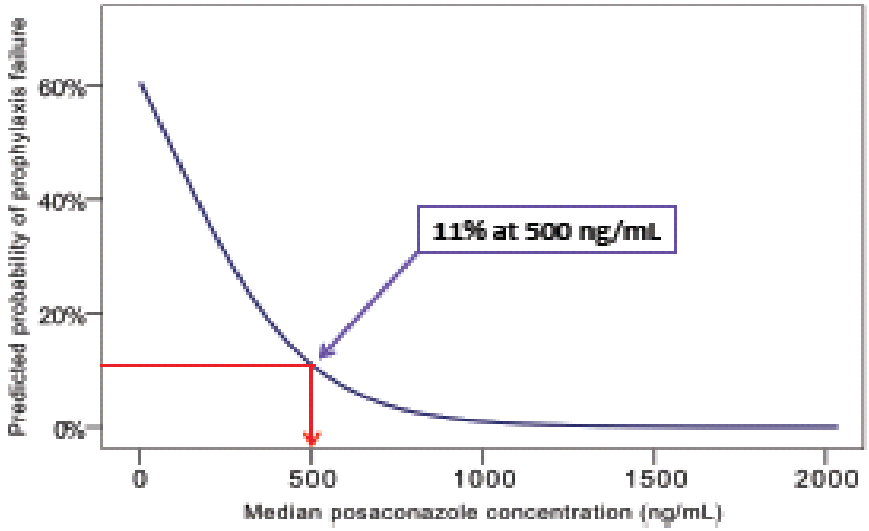
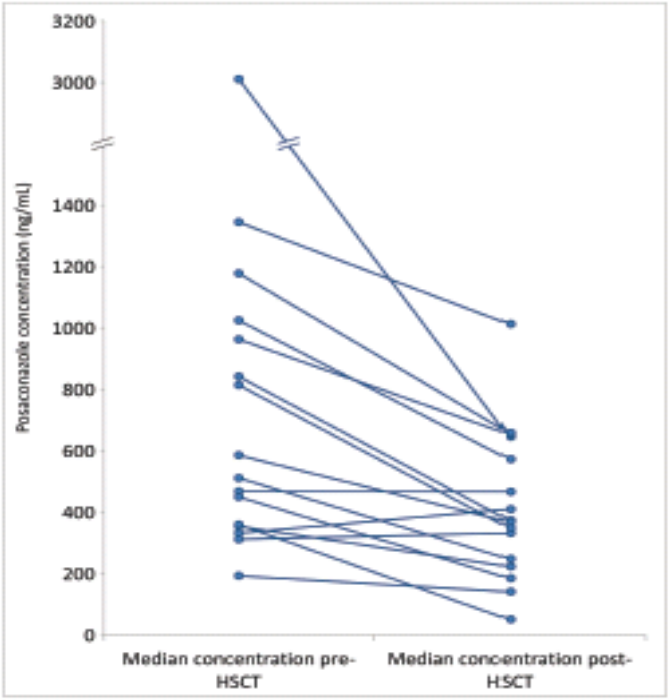


Figure 4 – Pre- and post-HSCT concentrations (within 5 days)



Prophylaxie et relation concentration / efficacité : Documentée pour

A – Itraconazole

B – Itraconazole, Voriconazole

C – Itraconazole, Voriconazole, Posaconazole

D - Aucun

Facteurs de variation des concentrations des antifongiques azolés chez les patients d'hématologie

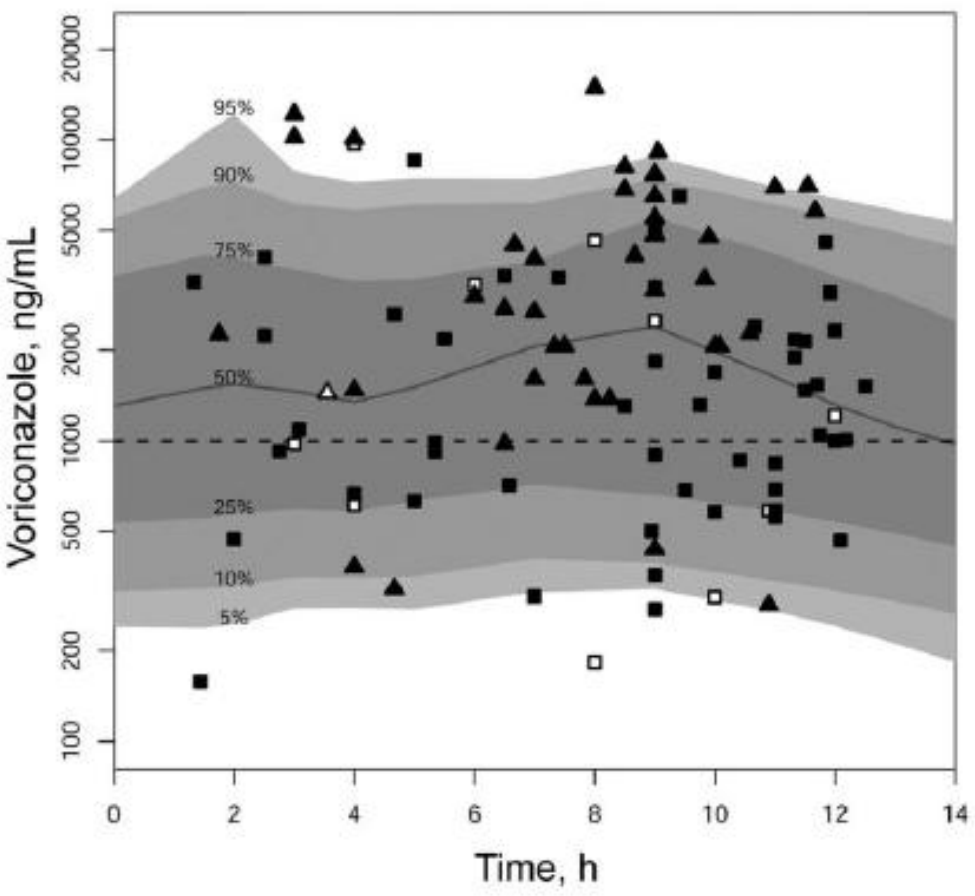
Voriconazole chez des patients allogreffés de moelle

	All	Initial	200 mg BID	300 mg BID
N	41	25	34	7
Range	0,2 - 6,8	0,2 - 6,8	0,2 - 6,8	0,6 - 6,6
Median	1,6	1,2	1,1	2,1
Mean	2,1	1,9	2,0	2,5
SD	1,8	1,6	1,8	1,9
< 0,5 mg/L	6 (15%)	3 (12%)	**6 (18%)**	**0 (0%)**
< 1 mg/L	15 (37%)	10 (40%)	**14 (41%)**	**1 (14%)**

Dose : ↗ si conc < 0,5 mg/L ; ↘ si conc > 7 mg/L

Trifilio, Bone Marrow Transplant, 2005

Voriconazole en pédiatrie (curatif)



n= 46 (0,8 à 20,5 ans)
26% infections prouvées
15% infections probables

- 207 prélèvements

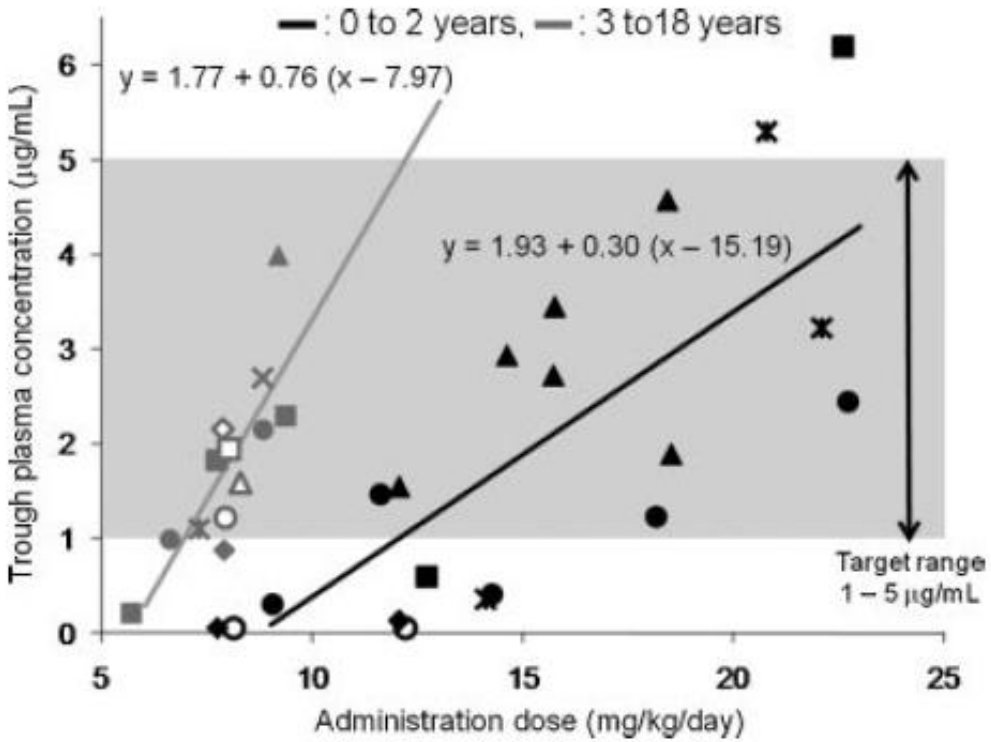
- A la dose de 7 mg/kg 2x/j
Cmin < 1 mg/L pour 66% des patients

Neely, CID, 2010

Voriconazole : prophylaxie en pédiatrie

Posologie recommandée :

- 5 mL x 2/j soit 200 mg x 2/j PO (Karlsson, AAC, 2009)
- 7 mg/kg x 2/j en IV



Prophylaxie primaire
n=16 (6 < à 3 ans)
7 LAL, 3 LAM
33 prélèvements

Shima, Pediatr Blood Cancer, 2010

A novel twice daily posaconazole dosing algorithm for children with CGD results in adequate exposure

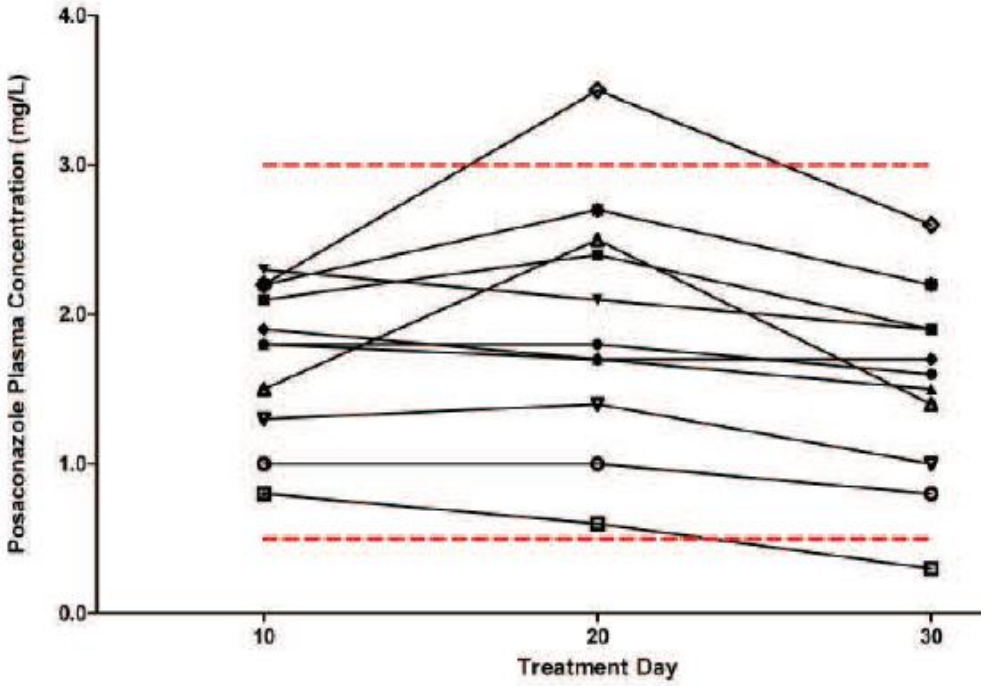
Marieke E.B. Welzen[1], Roger J.M. Brüggemann[1,2,*], J. Merlijn van den Berg[3], Heleen W. Voogt[3], Jos H. Gilissen[1], Dasja Pajkrt[3], Nigel Klein[4], David M. Burger[1,2], Adilia Warris[1,2]

50 YEARS ICAAC

A POS C_{trough} of at least 0.5 mg/L was pursued for adequate prophylaxis. If POS C_{trough} was lower, the dose was doubled and accompanied by repeated dietary advice. If POS C_{trough} was > 3.0 mg/L, the dose was lowered by 50%.

Table 1: Dosing algorithm for POS

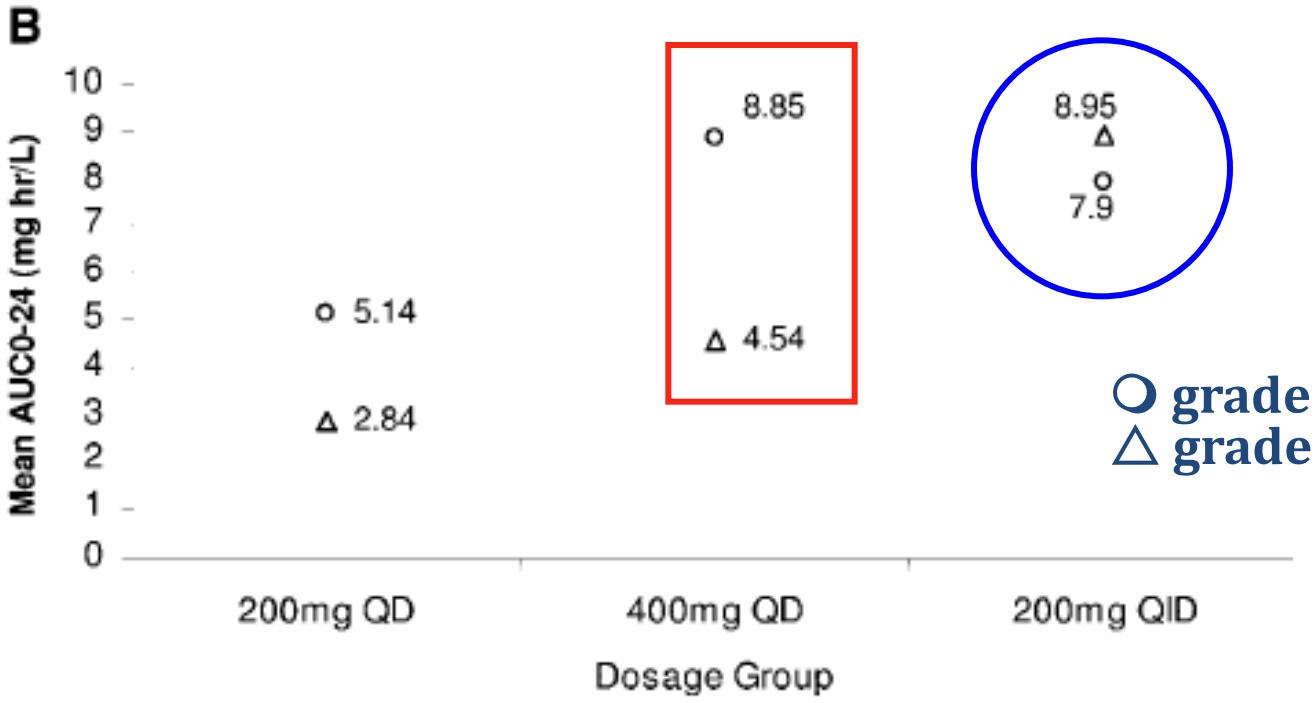
Body Weight	Dose (twice daily)
10-14 kg	120 mg
15-19 kg	160 mg
20-24 kg	200 mg
25-29 kg	220 mg
30-34 kg	260 mg
35-39 kg	280 mg
≥ 40 kg	300 mg



The children using once daily ITZ prophylaxis prior to the study chose to continue with the twice daily regimen of POS after the trial.

Posaconazole et mucites

- 30 patients
- autogréffés de moelle osseuse
- neutropéniques

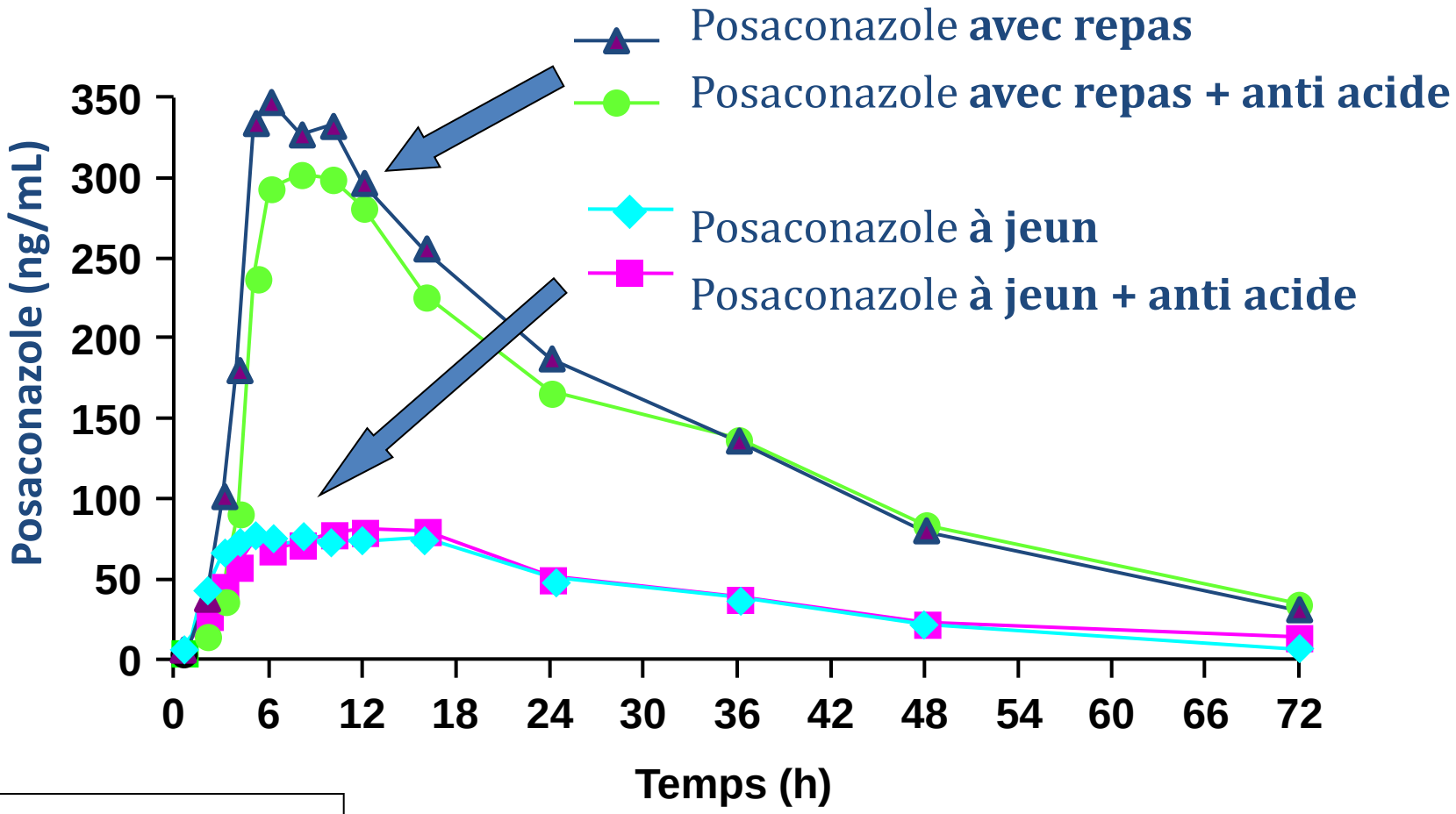


❍ grade 0
△ grade 1 et 2

n = 8 n = 15 n = 7

Gubbins, AAC, 2006

Posaconazole : effet de l'alimentation et du pH



n= 12 volontaires sains
dose = 200 mg

Courtney, AAC, 2004

Posaconazole Pharmacokinetics in Critically Ill Patients

Ray J[1], Campbell L[2], Rudham S[3], Reynolds C[3], Nguyen Q[4] and Marriott D[4]

Table 1: Information on study drug administration and plasma concentration.

	Regimen	
	400mg twice daily	200mg four times daily
C_{max}	113 ng/ml (74-126)	69 ng/ml (39-105)
T_{max} (first dose)	9 h	5 h
Steady state concentration (C_{min}) Day 4 Day 7	 187 ng/ml (86-390) 167 ng/ml (104-340)	 115 ng/ml (84-157)
First dose systemic exposure (AUC_{0-t})	789 ng.hr/ml	299 ng.hr/ml
Steady state data missing:	4	5
Died before completion	2	2
Drug stopped by primary team / patient transferred out of ICU	0	3
Poor absorption of feeds	2	0
>250ng/ml achieved in study (day 7)	2 of 9	1 of 9

Regimen	400mg twice daily	200mg four times daily
Total patients	13	14
Male	8	11
Age	56.8 +/- 17.3 (17-89)	44.8 +/- 22.7 (31-83)
APACHE III	74.62 +/- 38.69 (22-161)	72.62 +/- 35.32 (19-129)
Indication: prophylaxis	11	11
Indication: treatment	2	3
Use of PPI	All	All
Use of phenytoin	2	5
Median pH of gastric aspirates	7	7

Posaconazole : impact des conditions d'administration (AUC)

pH gastrique

400mg SD à jeun	400mg SD + boisson acide	400mg SD + IPP	400mg SD + boisson acide + IPP
réf	+70%	-32%	-21%

Posologie

400mg BID à jeun	400mg BID + Supplément nutritionnel	200mg QID à jeun	200mg QID + Supplément nutritionnel
réf	+66%	+160%	+157%

Repas gras

400mg SD à jeun	400mg SD Avant	400mg SD Pendant	400mg SD Après
réf	+111%	+382%	+387%

Motilité gastrique

400mg SD + Supplément nutritionnel	400mg BID + Supplément nutri + métoclopramide	400mg BID + Supplément nutri + lopéramide
réf	-19%	+11%

Krishna, AAC, 2009

Posaconazole

Etude rétrospective

	Prophylaxie N=36			Traitement curatif N=18			Total N=54
	<500 ng/ml	≥500 ng/ml	p	<500 ng/ml	≥500 ng/ml	p	
n (%)	16 (44)	20 (56)		4 (22)	14 (78)		
Age [mean (SD)]	44.1 (17.6)	52.5 (11.6)	0.095	31 (7.3)	44 (16.3)	0.15	48.7 (15.0)
BMI en kg/m² [mean (SD)]	21.6 (3.0)	24.3 (4.2)	0.055	15.8 (5.5)	22.6 (4.0)	0.07	23.2 (4.0)
Désordres digestifs n (%)	10 (63)	6 (30)	0.051	3 (75)	3 (21)	0.083	22 (41)
Diarrhée n (%)	10 (63)	4 (20)	0.0093	3 (75)	1 (7)	0.018	18 (33)
Mucites n (%)	6 (37.5)	0	0.0041	0	0		6 (11)
BMT n (%)	13 (81)	14 (70)	0.7	1 (25)	4 (28)	1	32 (59)
GVHD n (%)	12 (75)	13(65)	0.7	1 (25)	3 (21)	1	29 (54)

Lebeaux, AAC, 2009

Suivi thérapeutique du posaconazole

↳ 133 dosages entre Juillet 2006 et Juillet 2007

	DR1 400mgx2/j	DR2 200mgx3/j
Patients (n)	21	50
Echantillons (n)	38	95
$Cmin_{ss}$ (mg/L) m±SD , range médiane	0,63 ± 0,48 (0,1-2,57) 0,62	0,66 ± 0,51 (0,1-2,60) 0,54

La comparaison des $Cmin_{ss}$ nécessite la prise en compte de la différence d'apport journalier.

Padoin, RICAI, 2007

L'optimisation des traitements fongiques azolés vous paraît la plus difficile pour :

A – Voriconazole

B – Posaconazole

Comment adapter la posologie de l'antifongique azolé ?
Voriconazole - Posaconazole

Voriconazole

Mesure de la Concentration Résiduelle dès J2 après la dose de charge

Cible : idem curatif (>1 à 5 mg/L)

Si conc > à 5 mg/L : Réduction de posologie

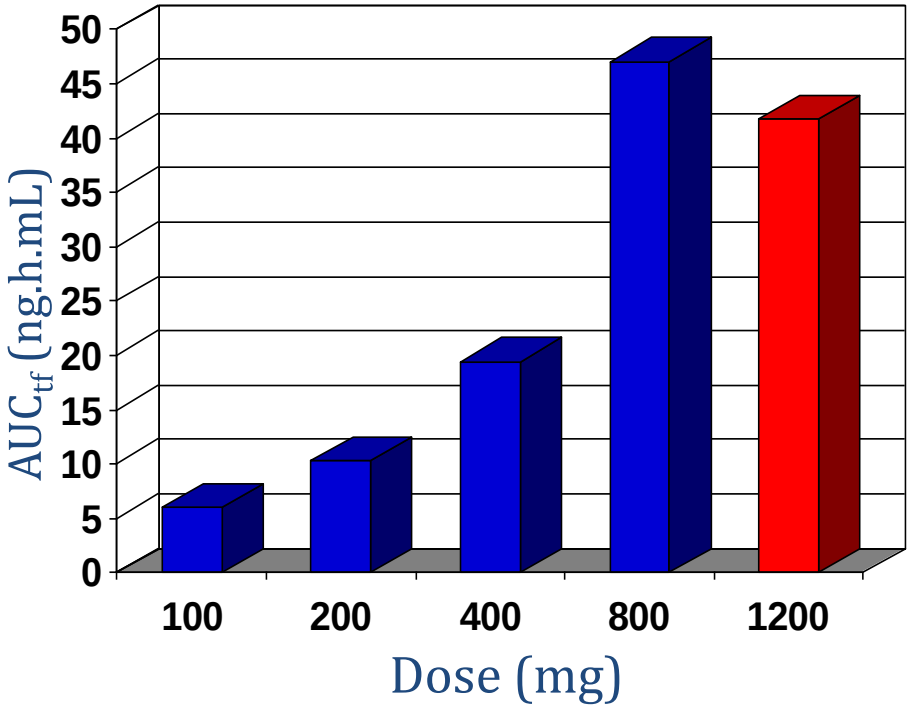
- **voie orale : réduction de 50 mg puis contrôle J3**
- **voie IV : réduction de 1 mg/kg puis contrôle J3**

Si conc < à 1 mg/L : Augmentation de posologie

- **voie orale : augmentation de 50 mg puis contrôle J3**
- **voie IV : augmentation de 1 mg/kg puis contrôle J3**

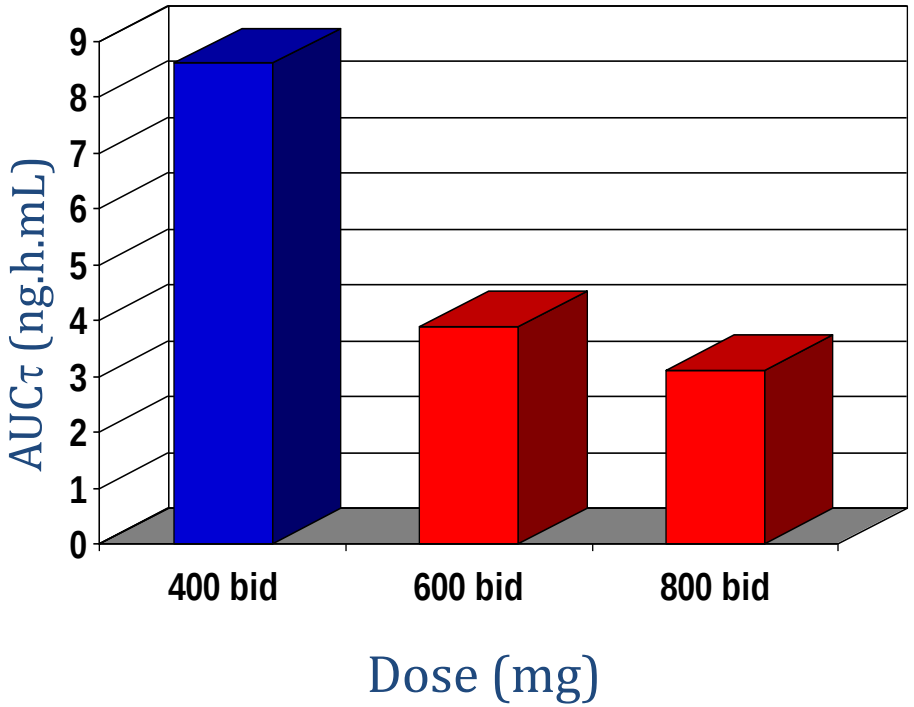
Absorption saturable du Posaconazole

Volontaire sain (dose unique)



Courtney, AAC, 2003.

Patient neutropénique (dose répétée)



Ullmann, AAC, 2006.

Dose de charge non réalisable

Suivi thérapeutique du posaconazole

↳ 820 dosages entre Juillet 2006 et Décembre 2009

	200mg x3/j	400mg x2/j	200mg x4/j	400mg x3/j
Echantillons	375	198	45	13
$Cmin_{ss}$ (mg/L) m±SD , médiane	0,71 ± 0,81 0,50	0,78 ± 0,69 0,69	0,68 ± 0,87 0,34	1,1 ± 0,53 1,2

Padoin, 2010

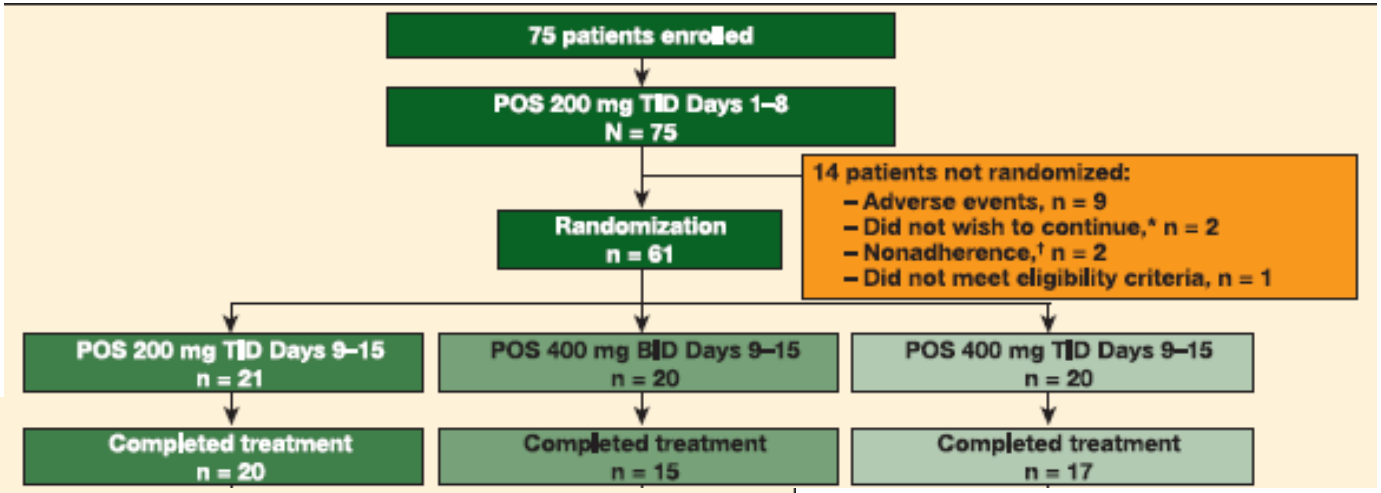
Pharmacokinetics of Different Dosing Strategies of Oral Posaconazole

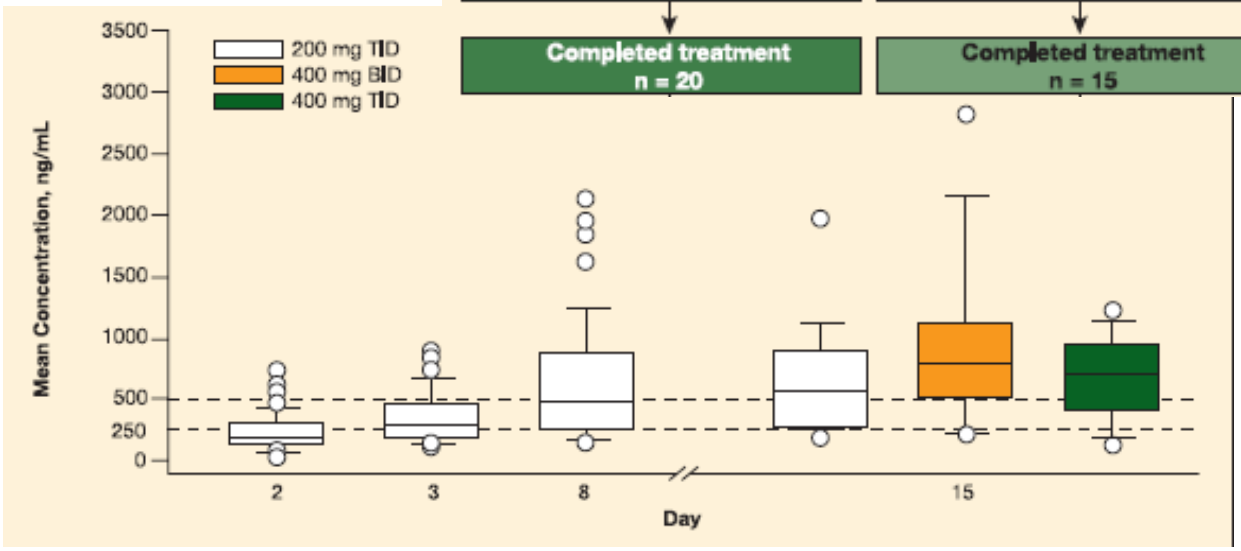
O. A. Cornely,[1,2] D. Helfgott,[3] G. Krishna,[4] L. Ma,[4] P. Carmelitano,[4] M. Martinho,[4] M. McCarthy[4]

50 YEARS ICAAC

Patients

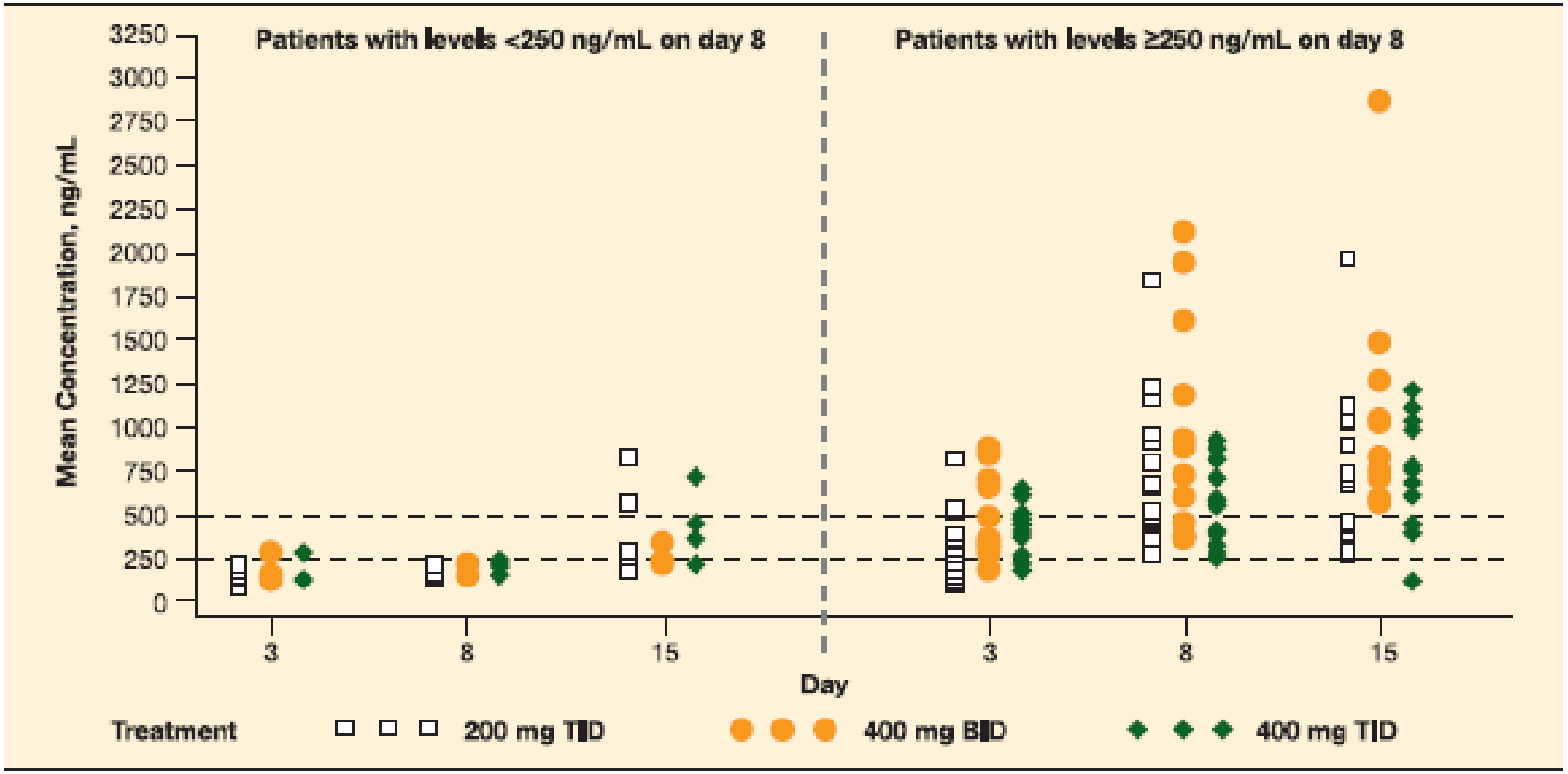
- 75 patients ≥18 years of age undergoing chemotherapy for acute myelogenous leukemia
- All patients at high risk for both of the following:
  - Poor absorption of enteral medication based on the effects of cytotoxic chemotherapy (evidenced by, but not limited to, mucositis, nausea, vomiting, and diarrhea)
  - IFI based on anticipated or documented prolonged neutropenia (absolute neutrophil count <500/mm³ [0.5 × 10⁹/L])





Pharmacokinetics of Different Dosing Strategies of Oral Posaconazole

O. A. Cornely,[1,2] D. Helfgott,[3] G. Krishna,[4] L. Ma,[4] P. Carmelitano,[4] M. Martinho,[4] M. McCarthy[4]



Conclusions: The mean plasma concentrations on Days 3 and 8 exceeded the PK parameters of interest. Day 3 levels appear to be predictive of Day 8 levels. There appears to be a subset of subjects who have low mean POS plasma concentrations, and a change in dosing regimen on Day 9 did not lead to higher exposures in these "poor absorbers" on Day 15.

Posaconazole

Mesure de la <u>Concentration Résiduelle</u> pas avant J5

<u>Cible</u> : > 0,5 mg/L

Si conc < à 0,5 mg/L :

Augmentation de la posologie et/ou fractionnement

- **<u>200 mg x 4/j</u>**
- **<u>300 mg x 3/j</u>**
- **<u>400 mg x 3/j</u>**

Contrôle à J5 après modification de la posologie

Que faire en cas de concentration encore « faible » ?

Le Suivi Thérapeutique Pharmacologique est une aide concrète dans la prophylaxie des infections fongiques en hématologie

A – OUI

B – NON

C – Ne sait pas

Impact des données tissulaires et *in vitro* sur le Suivi Thérapeutique Pharmacologique des antifongiques azolés

Cinétique Pulmonaire

Itraconazole

Conte, AAC, 2004

26 volontaires sains
200 mg x 2 /j (5j)
LBA : 4, 8, 12, 16, 24h

Cmax Itraco (mg/L)
Plasma 2,1 ± 0,8
ELF 3,3 ± 1,0
AC 0,5 ± 0,8

Cmax OH-Itraco
Plasma 1,0 ± 0,9
ELF 5,5 ± 2,9
AC 6,6 ± 3,1

AUC_{AC}/CMI_{90} =
Itraco 51
OH-Itra 67
= 118

Posaconazole

Conte, AAC, 2009

25 volontaires sains
400 mg x 2 /j (8j)
LBA : 3, 5, 8, 12, 24h
Reco. Alimentaires +++

Cmax (mg/L)
Plasma 2,1 ± 0,9
ELF 1,9 ± 1,3
AC 87,7 ± 65,0

$AC_{conc}/Plasma_{conc}$ = 44.3

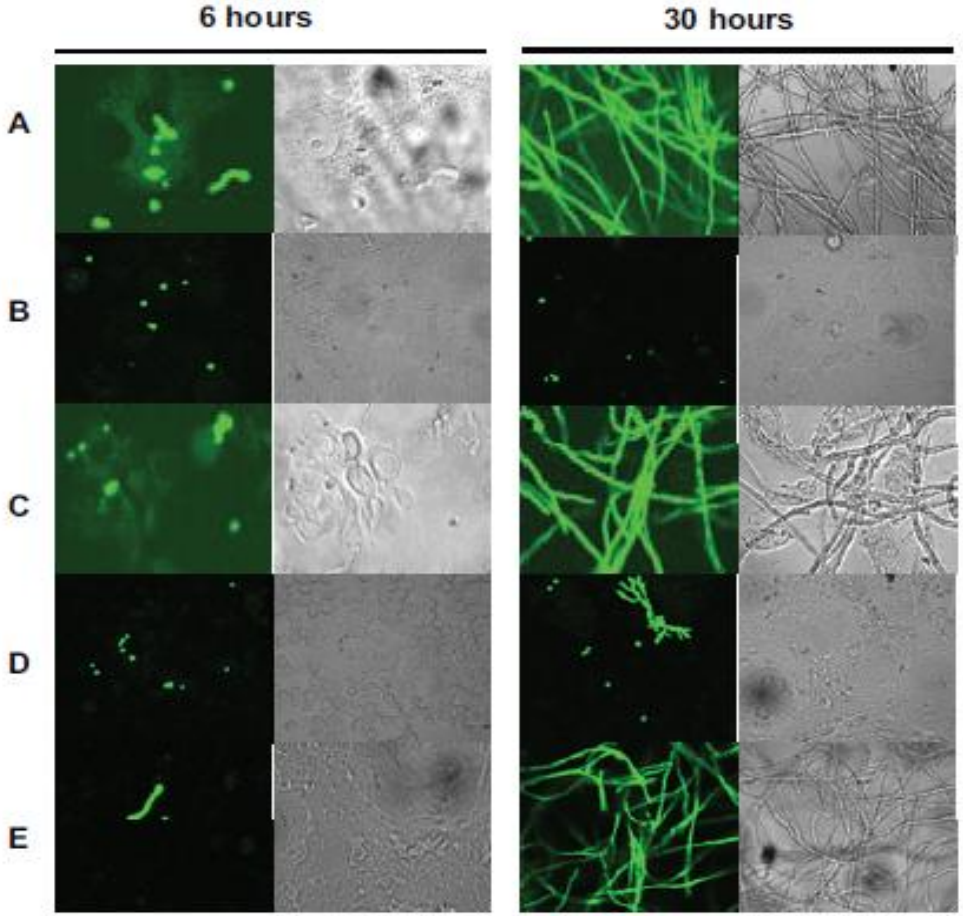
AUC_{AC}/CMI_{90} = 2 860

Effect of Cell-Associated Antifungal Agents on Inhibiting *Aspergillus fumigatus*

P Campoli [1*], Q Al-Abdallah[1], R Robitaille[2], NV Solis[4], M Laverdiere[3], SG Filler[4] and DC Sheppard[1]

50 YEARS ICAAC

A549 pulmonary epithelial cells were exposed to varying concentrations of posaconazole, voriconazole, caspofungin or amphotericin B for 4 hrs. The drug was then removed, the cells were washed and then infected with conidia of AFstrain Af293 in a microtiter assay. Minimal inhibitory concentrations were determined for cells exposed to antifungals and compared with the MICs of free drug in RPMI medium.



A) Drug free A549 cells,

B) A549 cells were loaded with posaconazole (2ug/ml),

C) A549 cells were loaded with voriconazole (8ug/ml),

D) Macrophages were loaded with posaconazole (2ug/ml

E) Macrophages were loaded with voriconazole (8ug/ml).

Campoli, AAC, 2011

Ces dernières données remettent- elles en cause le STP du Posaconazole ?

A : OUI

B : NON

C : ne sait pas