Treatment of invasive aspergillosis

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Infectious Diseases Clinic

SBIMC
8 November 2012
Amphotericin B liposomiale (Ambisome®)

Triazoles

Polyens

Amphotericin B lipid complex (Abelcet®)

Echinocandins

Caspofungin

Anidulafungin
Targets of systemic antifungal agents

Dodds Clin Infect Dis 2006; 43: S28-39
Primary treatment
First line: voriconazole

Targets ergosterol synthesis by inhibiting the fungal cytochrome P450-dependent enzyme lanosterol 14-a-demethylase → altered cell membrane function and cell death or inhibition of cell growth and replication

- First line treatment for invasive aspergillosis

IDSA guidelines. Clin Infect Dis 2008; 46, 327-60
Voriconazole vs Amphotericin B

- Randomized controlled trial of primary treatment for invasive aspergillosis
- Shift from AmB to OLAT (other licenced antifungal therapy)

277 evaluable patients
Voriconazole is superior to deoxycholate amphotericin B

Herbrecht et al. NEJM, 2002, 347, 408
Voriconazole

Efficacy of voriconazole also demonstrated in

• pediatric and adult patients
• with IA refractory or intolerant to conventional antifungal therapy

Denning Clin Infect Dis 2002; 34, 563-71;  
Perfect Clin Infect Dis 2003; 36, 1122-31;  
Walsh Pediat Infect Dis J 2002; 21: 240-8
Second line or salvage therapy

Lipid formulations of amphotericin B

Caspofungine

Posaconazole

(itraconazole)
Amphotericin B

- Act by binding to ergosterol (the principal sterol in the cell membrane of most medically important fungi) leading to the formation of ion channels and fungal cell death.

- Amphotericin B deoxycholate: not available anymore
- ABLC (Abelcet ®), L-AMB (Ambisome ®)

- Both preferentially distribute to reticulo-endothelial system tissues and functionally spare the kidney

- NB: most Aspergillus terreus are resistant in vitro and in vivo to AMB (also A. lentulus, nidulans, ustus, versicolor)
Lipid formulations of AmB

- Response rate +/- 40%

- Second line for patients who are intolerant of or refractory to voriconazole or patients with hepatotoxicity or other contraindications to voriconazole

- Which dose?

- Higher dosages required for equivalent efficacy:
  - ABLC (Abelcet®): 5 mg/kg,
  - L-AMB (Ambisome®): 3-5mg/kg
AmbiLoad study

No advantage to higher doses but higher toxicity

Rate of survival

Hematological malignancies: 93% of patients
Neutropenic at baseline: 73% of patients

Cornely Clin Infect Dis 2007; 44; 1289-97
Caspofungine (Cancidas®)

- Act by noncompetitive inhibition of the synthesis of 1,3-\(\beta\)-\(\beta\)-glucan, a polysaccharide in the cell wall of many pathogenic fungi
- Dose-proportional plasma pharmacokinetic
- Indicated in patients with invasive aspergillosis that is refractory to or intolerant of other approved therapies (Maertens Clin Infect Dis 2004; 39, 1563-71)
- Response rate +/- 40%
- Higher response (50%) in pulmonary aspergillosis than in disseminated aspergillosis (23%)
- Few adverse events (discontinuation of the drug in only 2.7% of 1951 patients) and few drug-drug interactions
<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>DRUG</th>
<th>REFRACTORY</th>
<th>INTOLERANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DENNING</td>
<td>VORICONAZOLE</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>FDA-FILE</td>
<td>CASPOFUNGIN</td>
<td>40%</td>
<td>56%</td>
</tr>
<tr>
<td>LISTER</td>
<td>ABLC</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>MEHTA</td>
<td>ABLC</td>
<td>40%</td>
<td>56%</td>
</tr>
<tr>
<td>WALSH</td>
<td>ABLC</td>
<td>52%</td>
<td>57%</td>
</tr>
<tr>
<td>WINGARD</td>
<td>ABLC</td>
<td>49%</td>
<td>53%</td>
</tr>
<tr>
<td>MILLS</td>
<td>AMBISOME</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>OPPENHEIM</td>
<td>ABCD</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>WHITE</td>
<td>ABCD</td>
<td>23%</td>
<td>49%</td>
</tr>
</tbody>
</table>
• Low response rate: favourable response (complete and partial) 33% (95% CI 21-46)

• The role of the severity of the underlying disease was quite evident in this study.
First-line treatment of invasive aspergillosis

### Table 3. First-line Treatment of Invasive Aspergillosis: Prospective Controlled Trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>N=</th>
<th>Design</th>
<th>Treatment</th>
<th>MDST (range)</th>
<th>Response (CR+PR)</th>
<th>Survival week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbrecht 2002 NEJM</td>
<td>277</td>
<td>op, rd</td>
<td>AmB Desoxycholate 1-1.5 mg/kg</td>
<td>10 (1-84)</td>
<td>31.6%</td>
<td>57.9%</td>
</tr>
<tr>
<td>Cornely 2007 CID</td>
<td>201</td>
<td>db, rd</td>
<td>Vori 2x6mg/kg d1 and 2x4 mg/kg d2+ i.v.*</td>
<td>77 (2-84)</td>
<td>52.8%</td>
<td>70.8%</td>
</tr>
<tr>
<td>Cornely 2007 CID</td>
<td>201</td>
<td>db, rd</td>
<td>LAmB 3mg/kg (d1-14)</td>
<td>14 (1-60)</td>
<td>50%</td>
<td>72%</td>
</tr>
<tr>
<td>Herbrecht 2010 BMT **</td>
<td>24</td>
<td>op, sa</td>
<td>LAmB 10 mg/kg (d1-14) op 3mg/kg d 15+</td>
<td>15 (1-57)</td>
<td>46%</td>
<td>59%</td>
</tr>
<tr>
<td>Viscoli 2009 JAC #</td>
<td>61</td>
<td>op, sa</td>
<td>Caspofungin 70mg d1/50 mg d2+</td>
<td>24</td>
<td>33%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caspofungin 70mg d1/50 mg d 2+</td>
<td>15 (3-84)</td>
<td>33%</td>
<td>53%</td>
</tr>
</tbody>
</table>

**Abbreviations:** op = open, rd = randomized, db = double blind, sa = single arm, MDST = Median duration of study drug treatment in days, * a switch to oral voriconazole was allowed after day 7, **allogeneic cohort of patients, # hematological malignancies and autologous transplantation
Posaconazole

- Structural analog of itraconazole
- Large hydrophobic compound
- MIC90 of fungal pathogens: 0.5 mg/L
- Oral drug available
- Approved in Europe for salvage therapy of patients with IA who are refractory to AMB or itraconazole
- Global response at the end of treatment 42% for posaconazole

Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial

• Early initiation of antifungal therapy
• Voriconazole:
  – First line therapy
  – IV formulation for seriously ill patients
• Insufficient clinical data to support combination therapy as routine primary treatment of IA
• Reversal of immunosuppression (reduction in the dosage of corticosteroids) or recovery from neutropenia

• Surgical resection of Aspergillus-infected tissue in patients with lesions
  – that are contiguous with the great vessels or pericardium,
  – causing hemoptysis from a single focus, and
  – lesions causing erosion into the pleural space or ribs
In case of renal or liver dysfunction

- **Creatinine clearance < 50ml/min:**
  - Vorico: accumulation of cyclodextrine (IV) → use oral vorico.
  - Same dose of caspofungine
  - Lipid AmB: nephrotoxicity

- **Liver failure (cirrhosis)**
  - Child-Pugh A et B: 50% of the dose of vori and caspo (hepatic metabolism)
  - Child-Pugh C:
    - no data.
  - Lipid AmB: no dose reduction. ! Renal toxicity!
Salvage therapy in case of failure of voriconazole

- Change of class using an AMB formulation or an echinocandin (also in case of breakthrough IA in the context of azole prophylaxis)

- Combination therapy with drugs from different classes other than those in the initial regimen may be considered

- Most of the prospective studies of second-line therapy have been conducted by replacing the compound against which the infection is progressing. Whether both drugs should be administered simultaneously has seldom been prospectively studied
Combination therapy

• Echinocandin combined with either an azole or ampho B formulation
• Distinct mechanisms of action offer the possibility of synergistic activity
• Possibility of antagonism? Particularly when these drugs are given sequentially (drugs blocking ergosterol synthesis given before the polyenes)

• 8 comparative studies (one RCT and seven cohorts)
  – Pilot RCT (Combistral trial): liposomal AmB (3mg/kg) + caspofungine vs liposomal AmB 10mg/kg (total of 30 patients) (Caillot Cancer 2007; 110: 2740)
  – Different antifungal combinations
Prospective, randomised, double-blind clinical trial

Allo-HSCT recipients and patients with haematological malignancies

Proven or probable IA

Combination therapy was administered for 2-4 weeks; after 2 weeks, voriconazole monotherapy, to complete at least 6 weeks of antifungal treatment

Combination therapy \(\rightarrow\) trend towards improved overall survival in patients with proven or probable IA diagnosed after allo-HSCT or treatment of haematological malignancies.

In the subset of patients with antigen-diagnosed disease: the combination increased the rate of overall 6-week survival (statistically significant).

Marr et al. ECCMID 2012
Duration of antifungal therapy

- Not well defined

- Minimum of 6-12 weeks

- In immunosuppressed patients, therapy should be continued throughout the period of immunosuppression and until lesions have resolved

- CT scan at regular intervals
  - Frequency? Should be individualized
  - The volume of pulmonary infiltrates may increase for the first 7-10 days of therapy, especially in the context of granulocyte recovery (Caillot J Clin Oncol 2001, 19: 253-9)

- GM-driven therapy: to be evaluated in non hematological patients
TDM of antifungal drugs?

• 3 general criteria for TDM
  – Variable pharmacokinetics
  – Narrow therapeutic window
  – Established relationship between plasma drug concentration and either efficacy or toxicity

Antifungal triazoles
Serum concentrations variability

Inter and intra-patient variability in serum concentrations (adults and children)

• Impaired absorption

• CYP2C19 genetic polymorphism → Nonlinear pharmacokinetics

• Potential drug-drug interactions
Large inter-personnal variability

- TDM to avoid subtherapeutic levels in HSTC recipients
- 43 allogenic hematopoietic SCT: prophylaxis with VORI

**Figure 1.** Correlation between voriconazole dose and drug level ($r = 0.14; P = .05$).

**Figure 2.** Voriconazole levels in 15 patients in whom ≥4 values were available illustrating variability.

*Trifilio Blood 2006; 108, 806a*
• 52 patients treated with VORI (31 for IA)

• Loading dose: 12mg/kg/d; maintenance: 6.5 mg/kg/d (5-8)

• Trough levels (after a median of 5 days)

• A higher proportion of patients with levels ≤ 1 mcg/ml received oral VORI

Pascual CID 2008; 46, 201-211
1. Impaired absorption

- Volunteers:
  - Bioavailability 96%
  - Effect of food: delays absorption, decreases bioavailability
    → Empty stomach
  - Patients with enteral nutrition: discontinued during 1/3 of time period

- Decreased bioavailability in severely ill patients as compared to volunteers
  - LTX: 46% during the early postoperative period
  - CF patients: lower by 87% as compared to non CF patients

Han AAC 2010; 54: 4424-4431
Voriconazole pharmacokinetic variability in cystic fibrosis lung transplant patients

• Very low serum concentrations
  – Increased clearance (young age and enzymatic induction by high doses corticosteroids)
  – Decreased absorption

• Importance of TDM

• The risk of long under-dosed periods could justify, on a PK basis, the need for combination with an exclusive parenteral antifungal while waiting for azole relevant drug level.

Role of impaired absorption?

Considerable inter- and intrasubject variation

Single trough concentration may not be representative of a patient's average level

IV voriconazole in allogenic HSCT recipients

Loading dose 6mg/kg bid day 1, then 4mg/kg bid

Bruggemann J Antimicrob Chemother 2010; 65, 107-13
### IV voriconazole in ICU patients

#### Table 3

Steady-state pharmacokinetic parameters of voriconazole, estimated from the concentration–time data by
in critically ill patients (N = 18) with either normal renal function or moderate renal impairment.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Dose (mg/12 h)</th>
<th>C_{SS} (S.D.) (mg/L)</th>
<th>C_{min} 0 h (mg/L)</th>
<th>C_{min} 12 h (mg/L)</th>
<th>C_{max} (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>240</td>
<td>0.78 (0.88)</td>
<td>0.17</td>
<td>0.15</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>2.94 (1.10)</td>
<td>1.99</td>
<td>1.82</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>320</td>
<td>4.55 (1.10)</td>
<td>3.12</td>
<td>4.04</td>
<td>7.0</td>
</tr>
<tr>
<td>4</td>
<td>250</td>
<td>7.73 (1.51)</td>
<td>5.62</td>
<td>5.95</td>
<td>10.4</td>
</tr>
<tr>
<td>5</td>
<td>400</td>
<td>4.26 (2.56)</td>
<td>2.33</td>
<td>2.66</td>
<td>9.7</td>
</tr>
<tr>
<td>6</td>
<td>245</td>
<td>0.50 (0.65)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>200</td>
<td>1.51 (1.95)</td>
<td>0.08</td>
<td>0.18</td>
<td>1.9</td>
</tr>
<tr>
<td>8</td>
<td>200</td>
<td>6.03 (2.00)</td>
<td>4.01</td>
<td>3.6</td>
<td>5.5</td>
</tr>
<tr>
<td>9</td>
<td>320</td>
<td>1.78 (1.30)</td>
<td>0.55</td>
<td>0.72</td>
<td>4.7</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
<td>0.23 (0.24)</td>
<td>N/A</td>
<td>N/A</td>
<td>0.7</td>
</tr>
<tr>
<td>11</td>
<td>200</td>
<td>0.60 (0.25)</td>
<td>0.32</td>
<td>0.40</td>
<td>1.1</td>
</tr>
<tr>
<td>12</td>
<td>300</td>
<td>4.33 (2.42)</td>
<td>2.09</td>
<td>2.10</td>
<td>9.6</td>
</tr>
<tr>
<td>13</td>
<td>280</td>
<td>5.71 (1.98)</td>
<td>3.61</td>
<td>3.90</td>
<td>9.6</td>
</tr>
<tr>
<td>14</td>
<td>240</td>
<td>1.09 (1.23)</td>
<td>0.33</td>
<td>0.27</td>
<td>3.8</td>
</tr>
<tr>
<td>15</td>
<td>240</td>
<td>4.69 (3.71)</td>
<td>0.78</td>
<td>0.8</td>
<td>11.4</td>
</tr>
<tr>
<td>16</td>
<td>400</td>
<td>1.05 (1.29)</td>
<td>N/A</td>
<td>N/A</td>
<td>4.1</td>
</tr>
<tr>
<td>17</td>
<td>320</td>
<td>1.22 (1.89)</td>
<td>N/A</td>
<td>N/A</td>
<td>5.9</td>
</tr>
<tr>
<td>18</td>
<td>300</td>
<td>1.49 (0.74)</td>
<td>0.79</td>
<td>0.69</td>
<td>2.7</td>
</tr>
</tbody>
</table>

**steady state D 3-5**

*Myrianthefs Int J Antim Agents 2010*
2. Genotyping variation

- Genetic polymorphism in CYP2C19
  - Normal = homozygous extensive metabolizers
  - Heterozygous extensive metabolizers
  - Poor metabolizers:
    - 20% of non-Indian Asians
    - 5% of Caucasians or African-Americans

  → Up to 4 times higher serum Voriconazole concentrations

- Caucasians: about 75% are homozygous extensive metabolizers and have lower voriconazole concentrations

- Autoinduction of voriconazole metabolism at higher doses is possible → voriconazole trough levels seem to decrease over time without apparent explanation (Mulanovich J Infect 2007; 55, 129)

- Accounts for 30% of the intersubject variability in voriconazole PK
3. Drug-drug interactions

Voriconazole is both a substrate and an inhibitor of CYP isoenzymes

• Voriconazole is a substrate of CYP enzymes → concomitant drugs can affect voriconazole serum concentrations
  
  - **CYP inducers:** rifampin, rifabutin, phenytoin, barbiturates, efavirenz, protease inhibitors, ritonavir → low serum concentrations
  
  - **CYP inhibitors:** omeprazole, oral contraceptive → high serum concentrations

• Voriconazole is an inhibitor of CYP enzymes
  
  → can affect serum concentrations of other drugs
Exposure-efficacy relationship

- Numerous reports on a possible link between serum voriconazole concentrations and its efficacy
Voriconazole: PK parameters

Serum concentration

- **Cmax (peak)**
- **AUC**
- **Cmin (trough)**

- **AUC/MIC** = best predictor of treatment efficacy in murine candidiasis
- Trough level is a good marker
Voriconazole prophylaxis in HSTC recipients

- 43 allogenic hematopoietic SCT: prophylaxis with VORI
  - 6 breakthrough IFIs if trough $C^{\circ} < 2 \text{mg/L}$
  - 0 if $>2 \text{mg/L}$  \( p = 0.061 \)

**FIGURE 1.** Correlation between voriconazole dose and drug level \( (r = 0.14; \ P = .051) \).

**FIGURE 2.** Voriconazole levels in 15 patients in whom $\geq 4$ values were available illustrating variability.

*Trifilio Blood 2006; 108, 806a*

*Bone Marrow Transplantation (2007) 40, 451–456*
Response to antifungal therapy

- 6 patients with persistence or progression of IFI and VORI levels ≤1mg/L: if all 6, IFI responded after an increase in VORI doses

- 5 pts with VORI levels >1mg/L and lack of response to therapy:
  - Probable invasive candidiasis (1), probable IA (1), possible IFI (2), 1 breakthrough zydomycosis

\[ \text{MIC}_{90} 0.5-1\text{mg/L for the majority of pathogenic fungi} \]

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Voriconazole trough blood level</th>
<th>( n = 13 )</th>
<th>( n = 39 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to antifungal therapy</td>
<td>( \leq 1\text{mg/L} )</td>
<td>21 (10-120)</td>
<td>17.5 (10-180)</td>
<td>NS</td>
</tr>
<tr>
<td>Interval between start of voriconazole therapy and assessment, median days (range)</td>
<td>&gt;1\text{mg/L}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>7 (54) (^a)</td>
<td>34 (68)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>5</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistence</td>
<td>6 (46)</td>
<td>5 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>3 (23)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakthrough IFI</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

\(^a\) In 1 patient, comorbidities with rifampin resulted in low voriconazole blood levels.
70% probability of response at a VORI trough level of 1mg/L
Correlation between voriconazole concentration and survival

- 25 patients (5 HSCT) treated for IFI

- **Initial steady-state trough** vori concentration was the best predictor for associated IFI-related mortality
  - All patients died when initial trough concentration was < 0.35 mg/L
  - Other factor strongly associated with IFI mortality: immunosuppression
  - A median voriconazole concentration > 2.2 mg/L was the best predictor of microbiological and clinical success

*Miyakis Clin Microbiol Infect* 2010; 16, 927-33
Relationship with clinical response

Drug toxicity? Severity of the disease???

FIG. 1. Binomial data and quadratic logistic fit for investigator outcome versus the mean voriconazole plasma concentration for 825 patients. ○, Data points separated as clinical success or clinical failure; ---, spline (moving average); --, line of predicted fit; ---, upper and lower 95% confidence intervals. The curvature was significant at $P < 0.003$. 

Troke AAC 2011
Trough concentration/MIC

Trough 2-5

FIG. 3. Relationship between the estimated trough concentration/MIC ratio and the probability of clinical response.
Exposure-toxicity relationship

- Photopsia or disturbance of vision: the most frequent 30%
  - Concentration dependent
  - Transient and fully reversible → no TDM required

- Neurotoxicity and elevated liver enzyme levels
Safety of voriconazole therapy

Only weak correlation between VORI exposure and severity of hepatotoxicity

Pascual CID 2008; 46, 201-211
• Analysis of 28 treatment courses

• 6 pts presented with neurological adverse event (hallucination, encephalopathy, visual disturbance)
Effect of TDM on safety and efficacy

- Randomized, assessor-blinded, controlled, single center trial (110 patients)
- TDM (target range 1.0-5.5 mg/L) versus fixed standard dosage
- No difference in the incidence of adverse events (90% of the adverse events developed within 10 days after starting therapy)
- Discontinuation of VORI due to adverse events: 4 (TDM) vs 17% (no TDM) p: 0.02
- Complete or partial response: 81% (TDM) vs 57% (no TDM → both toxic and subtherapeutic levels) p= 0.04
- Korean patients → poor metabolizers: 13% (prolonged half-life) → TDM may be more useful in non Asian patients

Park Clin Infect Dis 2012; 55: 1080-7
TDM (Australian study)

- Multicenter retrospective study
- 201 patients-783 VORI trough concentrations

- < 1.7 mg/L → greater incidence of treatment failure 26% vs 7%
- > 5 mg/L: more neurologic adverse events (32% vs 1.2%)

- Low concentrations: increasing patient weight, oral administration, coadministration of phenytoin or rifampin
- High concentrations: increasing patient age, coadministration of proton pump inhibitor
- **Coadministration of glucocorticosteroids significantly reduces VORI concentrations**

Dolton AAC 2012; 56: 4793-9
Recommendations for TDM

- Efficacy: wide range for voriconazole trough concentrations required for efficacy: 0.35-2.2 mg/L → at least 1-2 mg/L

- Toxicity: increased risk of neurotoxicity (and perhaps hepatotoxicity) when trough concentrations > 5-6 mg/L

Optimal serum concentrations: Between 1 and 5.5 mg/L (2-4)
Persistently low serum concentration

Try OMEPRAZOLE !!

Critically ill patients

- Initial trough drug level within 48h after a loading dose
- Repeated drug level at the steady state

- In acute severe infection, combination therapy with an other drug until therapeutic vori serum concentration are obtained
Obese adults

- 8 healthy volunteers (BMI 46 kg/m²):
  - Positive correlation between lean body weight (stronger than TBW)
  - No adjustment of doses on the basis of body weight
TDM of voriconazole

Number of patients

Median: 2 mg/L

554 blood samples
March 2009 - December 2010
SOT recipients, corticosteroids

Serum concentration (mg/L)

29% 55% 15%
Erasme hospital: first 100 days of treatment

Patients with >4 serum concentrations
First 100 days
Vorico IV  Po

Ambisome
Posaconazole: absorption

- Only oral formulation available:
  - Dose-proportional PK with dose-related increases in exposure up to a total dose of 800mg/d (saturable absorption)
  - Optimally administered in divided daily doses (2-4 times/d)

- Administration
  - with food → mean AUC x 2.6 and Cmax x 3
  - With high-fat meal: bioavailability x 4 as compared with the fasting state

→ Administration of posa with high-fat meal or nutritionnal supplement

Posaconazole: absorption

pH acide drink
PPI

PK of posaconazole

• Great inter-individual and inter-patient variability of plasma posaconazole concentrations

• Plasma concentrations are lower when:
  – Proton pump inhibitors are administered concomitantly
  – Patients are compared to healthy individuals
  – Allogeneic hematopoietic stem cell transplant recipients are compared to non-transplant recipients
  – Patients have diarrhea

Krishna G et al. Pharmacotherapy 2008
Distribution of serum posaconazole levels

Figure 2  Distribution of serum posaconazole levels obtained by The Fungus Testing Laboratory, San Antonio, Texas, from December 26, 2007 through December 30, 2008. Reproduced from Thompson et al, 2009.104

Kontoyiannis Am J Medicine 2012; 125:825
Treatment of invasive fungal infections
Relationship between plasma concentrations and efficacy

Table 8. Posaconazole plasma concentration versus global response in patients with invasive aspergillosis (MITT subset).

<table>
<thead>
<tr>
<th>Quartile</th>
<th>No. of subjects(^a)</th>
<th>Plasma C(_{\text{max}}) Mean ng/mL, CV, %</th>
<th>Plasma C(_{\text{avg}}) Mean ng/mL, CV, %</th>
<th>No. (%) of responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>142, 51</td>
<td>134, 45</td>
<td>4 (24)</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>467, 27</td>
<td>411, 21</td>
<td>9 (53)</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>852, 15</td>
<td>719, 12</td>
<td>9 (53)</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>1480, 16</td>
<td>1250, 28</td>
<td>12 (75)</td>
</tr>
</tbody>
</table>

**NOTE.** C\(_{\text{avg}}\), average plasma concentration; C\(_{\text{max}}\), maximum plasma concentration; CV, coefficient of variation.

\(^a\) Data were available for 67 patients with available plasma concentrations of posaconazole.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>CYP Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>Inhibitor</td>
<td>3A4++, 2C19++, 2C9++</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Inhibitor</td>
<td>3A4++, 2C9+</td>
</tr>
<tr>
<td></td>
<td>Inducer</td>
<td>3A4+++</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Inhibitor</td>
<td>2C19++, 3A4++, 2C9++</td>
</tr>
<tr>
<td></td>
<td>Inducer</td>
<td>2C19++, 3A4+, 2C9+</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Inhibitor</td>
<td>3A4+++</td>
</tr>
</tbody>
</table>

Zaas AK, J Invasive Fungal Infec 2007;1:133
Posaconazole: drug-drug interactions

- Should not be administered with rifabutin, phenytoin, or cimetidine unless benefits outweigh risks

- Blood levels of immunosuppressive agents (ciclosporin, tacrolimus, sirolimus) should be monitored and doses adjusted as necessary

- Contraindicated for administration with: terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine, ergot alkaloids, and HMG-CoA reductase inhibitors

- Other drugs not tested but may result in significant interactions: rifampicin, carbamazepine, phenobarbital, primidone, H2 receptor antagonists and proton pump inhibitors, sirolimus, digoxin, calcium channel blockers, antiretroviral agents, vinca alkaloids, and benzodiazepines
Conclusions on efficacy

- Prophylaxis: too few patients developed IFDs to determine a plasma concentration target for prophylaxis.

Suggested concentrations targets
- 400 – 500 ng/ml for prophylaxis
- 500 – 1500 ng/ml for treatment

- Long elimination half-life and large volume of distribution → posaconazole accumulates in tissues, reaching concentrations far above those in plasma
Posaconazole concentrations in tissues

**ELF and alveolar cells**

25 healthy adults (Conte):
- up 40 times higher in alveolar cells than in plasma
- The concentrations persisted above the MIC90 of Aspergillus over the 12-hour dosing interval and for 24h after the last dose

**Monocytes and neutrophils**

Conte. Antimicr Ag Chemother 2009; 53, 703-7

Farowski Antimicr Ag Chemother 2010; 54, 2928-31
The future?

• IV formulation of posaconazole
• Isavuconazole?