Antimykotische Therapie und TDM: ECIL 6 Guidelines

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Disclosures

• Grants
  – Gilead, Merck, Sharp & Dohme, Pfizer

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  – Amplyx, Astellas, Basilea, Gilead, Merck, Sharp & Dohme and Schering-Plough

• Speakers’ bureau
  – Astellas, Basilea, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon
ECIL Guidelines 2015: Triazole Antifungal Therapeutic Drug Monitoring

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ECIL - European Conference on Infections in Leukemia
- a joint initiative of EBMT, ICHS, EORTC and European Leukemia Net

http://www.kobe.fr/ecil/program2013.htm
What is Therapeutic Drug Monitoring (TDM)?

**Computation** of individual dosing recommendations based on drug concentrations in body fluids

Clinical presentation
- Patient-specific factors

Initial dosage

Determination of drug concentrations

Comparison to a target value

Adapted dosage

*empirical vs. based on Population-PK model(s)*
When does TDM make sense?

- if there is no readily available parameter of efficacy
- in drugs with high pharmacokinetic variability
- in drugs with small therapeutic window
- in populations at risk for increased toxicity
- established concentration/effect relationships
- established PK/PD target parameter / surrogate (i.e., $C_{\text{min}}$)
- validated, robust and rapid analytical method
Antifungal Agents and TDM

**Cell membrane**
- Polyenes
  - D-AmB
  - L-AmB
  - ABLC

- **Triazoles**
  - Fluconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
  - Isavuconazole

**Cell wall**
- Echinocandins
  - Caspofungin
  - Micafungin
  - Anidulafungin

**Nucleic acid synthesis**
- Flucytosine
Voriconazole
Voriconazole

- **Non-linear pharmacokinetics**

- **Complex metabolization**
  - Substrate/inhibitor of CYP2C9, 3A4, 2C19
  - *Genetic polymorphisms of CYP2C19*
  - *Changing metabolism rates (autoinduction)*
  - *Children: intestinal first-pass metabolism*

- **Number of relevant pharmacokinetic interactions**
  - **High variability in exposure**
  - **Toxicity issues with link to exposure**

* Zane et al., Clin Pharmacokinet 2014
VCZ – Relationship of Dose and Exposure

74 pts (0.2-18y; mean: 10.2y) / 101 courses of VCZ IV (4) and (15)/or (82) PO at median of 4.8 mg/kg BID (r, 2.2-17.4) for a median of 40 days (r, 6-1002)

- no predictable dose-concentration relationships
- high intra- and inter-individual variability in exposure
- quarter of samples with undetectable levels

<table>
<thead>
<tr>
<th>Voriconazole trough [mg/L]</th>
<th>No. (%) of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2</td>
<td>56 (22.3)</td>
</tr>
<tr>
<td>0.2 – 0.5</td>
<td>50 (19.9)</td>
</tr>
<tr>
<td>&gt; 0.5 – 1.0</td>
<td>39 (15.5)</td>
</tr>
<tr>
<td>&gt; 1.0 – 2.0</td>
<td>36 (14.3)</td>
</tr>
<tr>
<td>&gt; 2.0 – 5.0</td>
<td>50 (19.9)</td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>20 ( 8.0)</td>
</tr>
</tbody>
</table>

Pieper et al. JAC 2012
VCZ – Relationship of Dose and Exposure

Unpredictable accumulation of VCZ in a patient without any genetic risk factor in CYP2C19 / CYP 2C9 resulting in hallucinations and coma.
VCZ TDM – Correlation with Outcome in Patients with IFIs

- **trough levels** $\leq 1\text{mg/L}$ associated with treatment failure
- **trough levels** $\geq 5.5\text{ mg/L}$ assoc. with neurological toxicity

- **Blood levels** $> 1\text{ mg/L}$ reached after increasing the dosage with complete resolution of infection in all 6 cases

Pascual et al. CID 2008
VCZ TDM – Correlation with Outcome in Patients with IFIs

- randomized assessor-blinded single center study in 110 pts (75% IFDs)
- no TDM vs. TDM (target conc. 1.0-5.5 mg/L) based on trough on day 4

Routine TDM of VCZ may reduce discontinuation due to AEs and improve the treatment response in invasive fungal infections
• Meta-analysis of 24 studies assessing relationship btwn. VCZ serum concentration and success / toxicity

• Pooled analysis demonstrated that
  
  • 72.4% of pts. with therapeutic serum concentrations vs. 63.1% in those with sub-therapeutic concentrations had successful outcome (P=0.001)
  
  • Pts. with therapeutic conc. (1.0–2.2 mg/L) more likely to have successful outcomes (OR 2.30; 95% CI 1.39–3.81)
  
  • Pts. with suprathерapeutic serum VCZ levels had 4-fold increased likelihood of toxicity (OR 4.17; 95% CI 2.08–8.36)
Luong et al.: Relationship between VCZ concentrations and successful outcome
**Luong et al.: Relationship between VCZ concentrations and toxicity**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TDM cut-off &gt; 4-6</th>
<th>TDM cut-off &lt; 4-6</th>
<th>OR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total Events</td>
<td>Total Weight</td>
<td>OR, 95% CI</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Bruggemann et al.</td>
<td>0 / 2</td>
<td>6 / 37</td>
<td>0.97 (0.04, 22.65)</td>
</tr>
<tr>
<td>Chu et al.</td>
<td>9 / 16</td>
<td>92 / 7.9%</td>
<td>2.00 (0.68, 5.85)</td>
</tr>
<tr>
<td>Dalton et al.</td>
<td>10 / 31</td>
<td>170 / 6.5%</td>
<td>40.00 (8.20, 195.08)</td>
</tr>
<tr>
<td>Imhof et al.</td>
<td>4 / 7</td>
<td>19 / 5.2%</td>
<td>11.33 (1.40, 92.06)</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>4 / 7</td>
<td>20 / 4.4%</td>
<td>16.00 (1.38, 185.41)</td>
</tr>
<tr>
<td>Matsumoto et al.</td>
<td>9 / 12</td>
<td>17 / 4.5%</td>
<td>48.00 (4.33, 532.30)</td>
</tr>
<tr>
<td>Mitsani et al.</td>
<td>2 / 9</td>
<td>74 / 6.6%</td>
<td>42.67 (3.81, 478.42)</td>
</tr>
<tr>
<td>Okuda et al.</td>
<td>8 / 9</td>
<td>19 / 4.5%</td>
<td>1.22 (0.55, 2.73)</td>
</tr>
<tr>
<td>Park et al.</td>
<td>18 / 39</td>
<td>63 / 8.6%</td>
<td>5.00 (1.02, 24.41)</td>
</tr>
<tr>
<td>Pascual et al.</td>
<td>5 / 16</td>
<td>36 / 6.5%</td>
<td>0.49 (0.11, 2.20)</td>
</tr>
<tr>
<td>Pieper et al.</td>
<td>5 / 77</td>
<td>24 / 6.5%</td>
<td>1.55 (0.18, 13.37)</td>
</tr>
<tr>
<td>Racil et al.</td>
<td>1 / 7</td>
<td>257 / 5.0%</td>
<td>59.33 (13.92, 252.93)</td>
</tr>
<tr>
<td>Soler-Palacin et al.</td>
<td>8 / 14</td>
<td>182 / 6.9%</td>
<td>5.25 (1.18, 23.46)</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>7 / 14</td>
<td>25 / 6.7%</td>
<td>1.73 (1.39, 2.16)</td>
</tr>
<tr>
<td>Tan et al.</td>
<td>145 / 486</td>
<td>2116 / 9.7%</td>
<td>4.17 (1.04, 16.62)</td>
</tr>
<tr>
<td>Ueda et al.</td>
<td>8 / 20</td>
<td>4 / 7.0%</td>
<td>4.17 (2.08, 8.36)</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

<table>
<thead>
<tr>
<th>Total events</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>243</td>
<td>565</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 71.15, df = 15 (P < 0.00001); I^2 = 79\%$

Test for overall effect: $Z = 4.02 (P < 0.0001)$
Pharmacology: What target levels are recommended?

**Voriconazole concentration-efficacy relationship**

- *Prospective* studies have reported trough concentrations of ≥ 1.5-2 mg/L are associated with near maximal clinical response in treatment of IFI \(^1\textendash}^6\)
- **Post-hoc analysis of Phase II/III clinical trials:**\(^4\)
  - Vor C\(_{\text{avg}}\)/MIC target > 2, or vori plasma 2-5 mg/L
  - Response rate: 74%

**Recommendation:** *voriconazole prophylaxis and treatment target:* > 1-2 mg/L (*AII*);

higher troughs (> 2) are recommended for severe infections or when there are concern of treating fungi with elevated MICs

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**Pharmacology:** What target levels are recommended?

**Voriconazole concentration-toxicity relationship**

Recommendation: voriconazole safety target: < 5.0-6.0 mg/L (AII);

- Patients without symptoms of clinical toxicity may not require dose reductions

- Maintenance of exposures near this threshold may be needed for severe infections (e.g., CNS infection) or when treating fungi with elevated MICs

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Voriconazole TDM approach

Pharmacology: When should concentrations be evaluated?

First trough sample 2-5 days (or after 5th dose including loading doses):

Trough should be repeated during second week of therapy to confirm patient in therapeutic range (1-6 mg/L):

Recheck trough 3-5 days if:
• Change in dose or IV to oral switch
• Change in clinical condition (e.g., uncontrolled IFI or suspected toxicity)
• New interacting drug is started or stopped

Detailed recommendations for dose adjustments
Population-Pk based computer programs at the door
Posaconazole
Posaconazole

- Linear pharmacokinetics up to 800 mg (S)
- No CYP-mediated hepatic metabolism inhibitor, but no substrate of CYP 3A4
- No toxicity issues, but issues with absorption
TDM for Posaconazole: Clinical Data, Prophylaxis

- Food, gastric pH, gastric motility, mucosal disease (mucositis, diarrhea) weight and concomitant chemotherapy all affect PK and explain PK variability of the suspension.

No significant relationship between exposure and preventative efficacy in large prophylaxis studies.

MIC90 values of *Aspergillus* spp and limited clinical data suggest a dosing target of ≥500 ng/mL; FDA and EMA agreed on a lower boundary of $C_{avg}$ of 500 ng/mL for dose finding studies with new formulations.

*References: Ullmann 06; Gubbins 06; Ullmann 07; Krishna 07; Cornely 07; Krishna 08; Lebeaux 09; Jang 2010; Kohl 2010; Walravens 2011; Vehreschild 2012; Dolton 2012; Assessment report EMA/159150/2014*
Posaconazole: Delayed Release Tablet

pH-sensitive, acid-resistant polymer matrix
- enhanced bioavailability, less variability in exposure

- Phase 1B dose-ranging multicenter PK study in 51 pts with AML/MDS
- 200 and 300 mg QD (d1: BID)
  - 300 mg QD attained prespecified exposure target (≥500 and ≤2500 ng/mL, d8) in 97% of pts (mean Cavg 1460 ng/mL; AR: 2.5)
  - Loading with 300 mg BID on d1 attained Cavg >500 ng/mL in all
- no safety issues

Krishna et al, AAC 2012; Krishna et al, JAC 2012; Kraft et al, AAC 2014; Duarte et al, AAC 2014
Plasma Exposures following Posaconazole Delayed Release Tablets

- 20 pts, median age 14.8 yrs (5-18;6<13), median BW 49 kg (21-85)
  - approved dose in 16, modified in 4 pts for median of 40 d (20-303)
  - total of 30 trough levels

Median trough concentration 1661 +/-1459 ug/L

Trough concentrations above target of 700 ug/l in 28/30 occasions
**Pharmacology:** What target levels are recommended?

**Posaconazole concentration- prophylaxis efficacy**

- Pharmacokinetic analysis of two pivotal prophylaxis trials utilizing suspension formulation did not report significant concentration-effect relationships 1,2
  - Median POS 0.61 mg/L (breakthrough IFI) vs. 0.92 mg/L (no breakthrough)

- Other monocentric studies reported concentration-response relationship between posaconazole plasma trough levels and risk of breakthrough infection 2-7
  - > 0.5 or 0.7 mg/L

**Recommendation:** prophylaxis target: > 0.7 mg/L (BII)

**Tablet formulation (or IV formulation) are preferred formulations to maximize probability of achieving target plasma levels (AII)**

Pharmacology: What target levels are recommended?

Posaconazole concentration- toxicity

- No relationship between adverse effects and plasma concentrations for oral suspension\(^1-^3\)
- Pharmacokinetic bridging studies for gastroresistant tablet and IV formulation used an upper plasma target of 3.75 mg/L\(^3\)

Recommendation: At present, insufficient data to recommend target trough for safety further data are needed

Pharmacology: When should concentrations be evaluated?

Posaconazole gastroresistant tablet and IV formulations

Up to 10% of patients receiving new posaconazole formulations may not achieve plasma targets > 0.7 mg/L. The percentage of patients not reaching treatment target (> 1 mg/L) will be higher.

It is unknown whether risk for inadequate exposures can be predicted based on observable clinical risk factors alone (e.g., mucositis, aGVHD). Therefore, TDM remains the most direct approach for identifying patients with suboptimal posaconazole plasma levels.

- Pending further data, TDM is still recommended in patients receiving posaconazole tablets or IV formulation for prophylaxis (CIII)
- TDM is recommended in patients receiving posaconazole tablets or IV formulation receiving treatment for suspected or documented fungal infection (CIII)
- TDM is indicated for patients receiving tablets or IV formulation in the setting of breakthrough or progressing infection unresponsive to treatment, treatment of pathogens with reduced susceptibility, or drug interactions (CIII) -- additional data are needed

Isavuconazole
Isavuconazole (BAL-4815)

Administered as BAL8557, a water-soluble pro-drug suitable for oral and intravenous administration

- Favorable PK properties
  - linear PK, long t ½, high tissue distribution
  - 98% bioavailability, not affected by pH or food
  - less PK variability versus voriconazole
- Interaction profile similar to other azoles
- Safety improved relative to voriconazole

Approved for inv. aspergillosis and mucormycosis

1 Schmitt-Hoffmann et al, AAC 2006;
2 Schmitt-Hoffmann et al, AAC 2006
Pharmacology: What target levels are recommended?

Isavuconazole-concentration efficacy

Isavuconazole package labelling:

12.2 Pharmacodynamics

Pharmacokinetic/Pharmacodynamic Relationship
In patients treated with CRESEMBA for invasive aspergillosis in a controlled trial, there was no significant association between plasma AUC or plasma isavuconazole concentration and efficacy.

TDM is indicated for patients receiving tablets or IV formulation in the setting of breakthrough or infection unresponsive to treatment, treatment of pathogens with reduced susceptibility, or in the setting of drug interactions (CIII)

additional data are needed
Conclusions
What did Groll say…

- Ample room for improvement in management of IFIs
- There is no rationale for TDM for polyenes and echinocandins
- TDM is an issue for antifungal azoles
  - strong recommendation for itraconazole and voriconazole
  - weak recommendation for new formulations of posaconazole and for isavuconazole
- Issues that need further clarification
  - optimum sampling schedule
  - models/ algorithms for dose modifications
  - situations in which to consider alternative agents