Prevention & Management of IFI-Mind the Gap(s)!
Integrated Symposium - TIMA 2019
Nice, Acropolis Convention Center, Nice, France

Is it time to rethink echinocandin dosing?
Russell Lewis
Associate Professor, Infectious Diseases
Department of Medical and Surgical Sciences
University of Bologna

Treatment of Candidemia / Invasive Candidiasis
Unmet Needs

Rezafungin for Treatment of Invasive Candidiasis
George R. Thompson III, MD
Associate Professor
Division of Infectious Diseases
Department of Internal Medicine
Department of Medical Microbiology and Immunology
University of California-Davis Medical Center

PREVENTION OF INVASIVE Fungal INFECTIONS IN VULNERABLE HOSTS
Prevention & Management of IFI- Mind the Gap(s)!

Integrated Symposium - TIMM 2019
Nice, Acropolis Convention Center, Nice, France
Welcome and Opening Remarks

Oliver A. Cornely MD, FACP, FIDSA, FAAM, FECMM

Director and Chair, Translational Research & Clinical Trials Center
University of Cologne

Consultant, Infectious Diseases
Director, European Mycology Excellence Center
University Hospital of Cologne
HOUSEKEEPING

Mobile phones

Question cards

Microphones
Mind The Gaps!

Epidemiology

Resistance

Drug-drug interactions

... to mention just a few ...
Vendredi, le 11 octobre en Europe

79 candidaemia cases \( \rightarrow \) TIMM is an orphan disease meeting

Dimanche, le 10 novembre \( \rightarrow \) We all love Sundays, but 29 dead by that Day 30 (37%)

Candidemia incidence is increasing

Non-albicans proportion is increasing
# Resistance

<table>
<thead>
<tr>
<th>Species</th>
<th>Resistance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. parapsilosis</em></td>
<td>Fluconazole</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>Azoles, echinocandins</td>
</tr>
<tr>
<td><em>C. auris</em></td>
<td>MDR → XDR → PDR</td>
</tr>
<tr>
<td><em>A. fumigatus</em></td>
<td>Azoles</td>
</tr>
<tr>
<td><em>A. flavus</em></td>
<td>Amphotericin</td>
</tr>
</tbody>
</table>
Drug-Drug Interactions

New drugs in oncology

- Are welcome advances
- Many increase risk for IFI
- Usually interact with triazoles
- Such interaction not evaluated in oncology drug development
Mind the Gaps!

16:50 - 17:05  PK/PD Optimized Echinocandin Dosing  Russel E. Lewis
17:05 - 17:20  Unmet Needs for Treatment of IC/Candidemia  Bart J. Kullberg
17:20 - 17:40  Rezafungin for Treatment of Candidemia/IC  George R. Thompson
17:40 - 18:00  Current Challenges for prophylaxis of IFI  Kieren Marr
18:00 - 18:10  Q&A  Panel
18:10 - 18:15  Closing Remarks  Oliver A. Cornely
Is it time to rethink echinocandin dosing?

Russell Lewis
Associate Professor, Infectious Diseases
Department of Medical and Surgical Sciences
University of Bologna
Disclosures

• Research support: Merck Inc.
• Advisory committees: Gilead, Cidara, F2G
“Medicine is a science of uncertainty, and an art of probability”

Sir William Osler, M.D. (1849-1919)
The uncertain science of antibiotic dosing

Dosing

- Site of infection
- Patient factors
- Drug characteristics
- Intrinsic activity
- Acquired resistance

Pharmacokinetics (PK)
- Exposure variability
- Toxicity

Pharmacodynamics (PD)
- MIC variability

PK/PD Index

Microbiologic effect

Clinical outcome

Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792
Echinocandin exposures are variable in critically-ill patients

- Pharmacokinetic point prevalence study (n=68 ICUs): ¹
  - Included patients receiving caspofungin/ anidulafungin
    - $C_{\text{max}}, AUC_{0-24}, C_{\text{min}}$ ~50% lower values than reported in healthy volunteers
    - $C_{\text{max}}, AUC_{0-24}, C_{\text{min}}$ ~40% lower values than reported in previous ICU PK studies

- Empirical micafungin in ICU patients with sepsis, organ failure and Candida colonization (EMPIRICUS trial): ²,³
  - Empirical micafungin 100 mg/day was not associated with improved fungal-free survival vs. placebo by day 28
  - Measured micafungin blood concentrations were lower than expected → increased clearance (low albumin) and obesity ⁴

Micafungin 100 mg/day probability of target attainment (PTA)*
A PK/PD autopsy of the EMPIRICUS trial

PTA* was ≥ 90% in *Candida albicans* and *Candida glabrata* infections, except when the MIC was ≥0.015 mg/L

**C. albicans** MIC=0.016 mg/L; SOFA < 10

**C. albicans** MIC=0.016 mg/L; SOFA ≥ 10 (25% decrease in clearance)

Median patient weight: 84.5 kg (48-141)

Echinocandin drug penetration at the site of infection
Intraabdominal abscess model

IP infection model: $1 \times 10^7 \ C\ albicans$ with sterile stool

Matrix-assisted desorption ionization mass spectrometry imaging technology


Liver lesions after single dose experiment
Echinocandin drug penetration at the site of infection

Intraabdominal abscess model multiple micafungin doses


Liver lesions after 2-3 micafungin doses
Drug distribution in liver after single dose CD101 at 20 mg/kg determined by MALDI MS Imaging

Rezafungin penetration at the site of infection

Zhao, Perlin et al, AAC July 2017
Dosing

Patient factors

Drug characteristics

Intrinsic activity

Acquired resistance

Exposure variability

MIC variability

Toxicity

PK/PD Index

Microbiologic effect

Clinical outcome

Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792
Where do we find echinocandin resistance?

- Bloodstream
- GI tract
Where do we look for echinocandin resistance?

- **Esophagus:** Lower drug concentrations, high inoculum, biofilms
- **Bloodstream:** High drug concentrations, low inoculum
- **Gut:** Low drug concentrations, high inoculum, biofilms?

Where do we look for echinocandin resistance?

Oral swab surveillance after ≥ 7 days of echinocandins

Acquired resistance in *C. glabrata* 21.6%

SENTRY 2006-2016, single center studies

Echinocandin resistance rate: 3-12%

FKS mutant *Candida* isolates detected in 24%

(6/25) patients exposed to echinocandins

*C. glabrata* 29%
*C. albicans* 14%

---

The GI tract as the major source of echinocandin resistance

$1.5 \times 10^8$ CFU C. glabrata $\rightarrow$ PIP/Tazo $\rightarrow$ Dexamethasome immunosuppression

Caspofungin 5 mg/kg (humanized dose)

$\leftrightarrow$ CFU in stool vs. control (FKS mutants in 10% mice)

No positive BC during caspofungin treatment

Organ dissemination in 60% of mice (No FKS mutants)
Mean small intestine-3.8 μg/mL
Mean large intestine-9.1 μg/mL

Caspofungin 20 mg/kg (4x humanized dose)

$10^7$-$10^8$ CFU/stool

Controls 50%

Controls 70% (No FKS mutants)

Organ dissemination in 30% of mice (ALL FKS mutants)
Mean small intestine-36.2 μg/mL
Mean large intestine-22.2 μg/mL

10^7-10^8 CFU/stool

No positive BC during caspofungin treatment

Organ dissemination in 60% of mice (No FKS mutants)
Mean small intestine-3.8 μg/mL
Mean large intestine-9.1 μg/mL

No positive BC (100% mice with FKS mutants)

Controls 50%

No positive BC during caspofungin treatment

Organ dissemination in 30% of mice (ALL FKS mutants)
Mean small intestine-36.2 μg/mL
Mean large intestine-22.2 μg/mL

Dosing

Patient factors

Drug characteristics

Intrinsic activity

Acquired resistance

Exposure variability

MIC variability

Toxicity

PK/PD Index

Microbiologic effect

Clinical outcome

Site of infection

Is our dosing optimized to address these problems?

Pharmacokinetics (PK)

Pharmacodynamics (PD)

Yes

Yes

Yes

Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792
Currently-recommended echinocandin dosing schemes were not developed from PK/PD principles

“An additional challenge was that there was no definitive information about the PK/PD relationship for pneumocandins, making dose selection less certain.”

What have we learned about echinocandin PK/PD from animal models?

Rabbit model of invasive candidiasis

Micafungin Cmax/MIC and AUC/MIC correlate with efficacy

Mean AUC_0-312 similar for all three regimens

Larger infrequent doses maximize echinocandin antifungal activity

Neutropenic rabbit model of invasive candidiasis

*C. albicans* MIC 0.125 mg/L (CLSI)

When AUC/MIC is equivalent, dosing regimens that achieve a higher Cmax/MIC exhibit improved killing

* P< 0.05 vs. control
Echinocandins are not fungicidal against *C. glabrata* in neutropenic models at currently recommended doses.

Humanized dosing, neutropenic murine model of *C. glabrata* fungemia (MIC 0.06 mg/L).

Clinical pharmacodynamic index identification for micafungin in esophageal candidiasis: Dosing strategy optimization

<table>
<thead>
<tr>
<th>Micafungin dosing regimen</th>
<th>Mycological response at EOT?</th>
<th>Clinical relapse at 2 weeks?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success (n=260)</td>
<td>Failure (n=56)</td>
</tr>
<tr>
<td>150 mg QD</td>
<td>145 (78.8)</td>
<td>39 (21.2)</td>
</tr>
<tr>
<td>300 mg QOD</td>
<td>115 (87.1)</td>
<td>17 (12.9)</td>
</tr>
</tbody>
</table>

\[ P = 0.056 \]

\[ P = 0.051 \]

The dosing regimen that achieves a higher Cmax/MIC was associated with improved clinical success and lower relapse rates.
Caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

Conclusion: Both dosing regimens were equivalent and safe

Time to clearance of blood cultures

Design hypothesis: Higher caspofungin dose is safe and non-inferior Δ <15%. Study was not powered to evaluate superiority of caspofungin higher dose

Multicenter double-blind trial of caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

Comparison of caspofungin vs. rezafungin PK/PD target attainment (C. glabrata MIC 0.25 mg/L)

Caspofungin (14 daily doses)

- MIC=0.25 for caspofungin. MIC=0.12 for CD101


Bader et al. Overcoming the Resistance Hurdle: PK-PD Target Attainment Analyses of Rezafungin (CD101) for Candida albicans and Candida glabrata. Submitted AAC 2018; revised with Phase 2 results.
Novel echinocandin dosing approaches during micafungin prophylaxis

• Intermittent administration of higher-dose micafungin (≥ 5 doses of 300 mg 2-3 times weekly) was well tolerated in patients with acute leukemia and allogeneic SCT recipients

• Intermittent higher-dose micafungin was safe in children

• Equivalent weekly AUCs have been confirmed for 300 mg twice weekly dosing of micafungin (3hr infusion) → possible 700 mg once weekly?

Summary

• Preclinical and clinical evidence suggest current echinocandin dosing approaches need revision for some patient groups

• Acquired echinocandin resistance can be detected at much higher frequency in the GI tract than bloodstream, and likely serves as a reservoir for future breakthrough infection

• Evidence that PK/PD optimization of echinocandin dosing might improve clinical efficacy, reduce relapse, and enhance dosing convenience
Thank you!

“The Great Wave of Candida”
Cristina Marcos

The Great Wave off Kanagawa
Katsushika Hokusai
Treatment of Candidemia / Invasive Candidiasis

Unmet Needs

Bart-Jan Kullberg, M.D.
Center for Expertise in Mycology Radboudumc/cwz
Radboud University Medical Center
Nijmegen, The Netherlands
Disclosures

- Scientific advisor for Amplyx, Cidara, and Scynexis
- Participated in CME with support from Cidara and Pfizer.
Case Study

- A 62 year-old woman underwent abdominal surgery for a cholangiocarcinoma
- Post-operative ICU stay, fever 39.6°C
- Piperacillin-tazobactam and vancomycin
- Possible suture leak
- Abdominal CT inconclusive
- Blood cultures (still) negative

What is the likelihood of invasive candidiasis?
How can we diagnose invasive (abdominal) candidiasis?
Should she have received antifungal prophylaxis?
Should she receive empiric antifungal therapy?
If so, aimed at which Candida species?
Unmet Needs

✓ Can we prevent invasive candidiasis in the ICU?
Antifungal prophylaxis in the ICU

- **Does it work?**
  - Yes, some reduction of incidence

- **Does it work well enough?**
  - No ... Less than optimal results:

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Prophylaxis</th>
<th>Reference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17%</td>
<td>10%</td>
<td>n.s. Ostrosky-Zeichner</td>
<td>2014</td>
</tr>
<tr>
<td>15%</td>
<td>8.5%</td>
<td>0.01 Pelz</td>
<td>2001</td>
</tr>
<tr>
<td>10%</td>
<td>4%</td>
<td>0.02 Garbino</td>
<td>2002</td>
</tr>
<tr>
<td>9%</td>
<td>2%</td>
<td>n.s. Eggimann</td>
<td>1999</td>
</tr>
</tbody>
</table>

- **Has it been associated with reduced mortality?**
  - No ... In none of the studies:

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Prophylaxis</th>
<th>Reference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14%</td>
<td>17%</td>
<td>n.s. Ostrosky-Zeichner</td>
<td>2014</td>
</tr>
<tr>
<td>12%</td>
<td>11%</td>
<td>n.s. Pelz</td>
<td>2001</td>
</tr>
<tr>
<td>41%</td>
<td>39%</td>
<td>n.s. Garbino</td>
<td>2002</td>
</tr>
<tr>
<td>50%</td>
<td>30%</td>
<td>n.s. Eggimann</td>
<td>1999</td>
</tr>
</tbody>
</table>
### MSG-01: Echinocandin prophylaxis in high-risk ICU patients

Randomised, double-blind, multicentre study of caspofungin vs. placebo

<table>
<thead>
<tr>
<th>Invasive candidiasis</th>
<th>Caspofungin</th>
<th>Placebo</th>
<th>Difference P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven/probable, after baseline</td>
<td>9.8%</td>
<td>16.7%</td>
<td>P=0.14</td>
</tr>
</tbody>
</table>

| Proven invasive candidiasis | 1.0% | 4.8% | P=0.11 |
| Mortality | 16.7% | 14.3% | P=0.35 |

Length of stay n.s.

**Conclusions:**
1. No support for antifungal prophylaxis among ICU patients
2. We are unable to identify the patient at risk for candidiasis

---

1 Modified intent-to-treat group: eligible patients without candidiasis at baseline, who received ≥1 dose of study drug
2 Caspofungin has not been licenced for prophylactic use
3 Probable candidiasis (EORTC/MSG): 2x β-glucan>80 AND clinical signs
Unmet Needs

✓ Can we treat invasive candidiasis in the ICU earlier?
Candidemia: Importance of early appropriate treatment

157 patients – 2001–2004
Initiation of antifungal therapy <12 to >48 h after culture sample
Morrell M, et al. AAC 2005

230 patients – 4 centres – 2002–2005
Initiation of fluconazole 0 to ≥3 days

446 patients – 2001–2009
Intent to treat: 31.6–36.3% - N.S.
Shown: when Rx for <24 h classified as inappropriate

Radboudumc
Empirical micafungin in ICU patients with sepsis, organ failure and *Candida* colonization

Randomised, double-blind, multicenter study of micafungin vs. placebo

- Non-neutropenic adult patients in ICU
- Mechanical ventilation ≥5 days
- Broad-spectrum antibiotics ≥4 days
- ≥1 Site colonized with *Candida* species
- New ICU-acquired sepsis
- ≥1 Additional organ dysfunction

<table>
<thead>
<tr>
<th>MITT$^1$, N=251</th>
<th>Micafungin (14 days)</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day Survival free of proven fungal infection</td>
<td>68%</td>
<td>60%</td>
<td>HR 1.35 (0.87-2.08)</td>
</tr>
<tr>
<td>Survival (d28)</td>
<td>70%</td>
<td>70%</td>
<td>HR 1.04 (0.64-1.67)</td>
</tr>
<tr>
<td>Invasive fungal infections</td>
<td>9%</td>
<td>12%</td>
<td>Δ 2.8% (-5.0, 10.8)</td>
</tr>
</tbody>
</table>

**Conclusions:**
1. No support for empirical antifungals among ICU patients
2. We are unable to identify the patient at risk for candidiasis

---

$^1$Modified intent-to-treat group: patients who received ≥1 dose of study drug


Radboudumc
Unmet Needs

✓ Are we able to identify the patient with invasive candidiasis?
Abdominal candidiasis – The missing 50%

2-year retrospective cohort, U Pittsburg Medical Center

<table>
<thead>
<tr>
<th>Patients</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidemia</td>
<td>161</td>
</tr>
<tr>
<td>Intraabdominal candidiasis</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraabdominal candidiasis</td>
<td></td>
</tr>
<tr>
<td>GI tract source</td>
<td></td>
</tr>
<tr>
<td>Secondary peritonitis/abscess (post GI leak, surgery)</td>
<td>103</td>
</tr>
<tr>
<td>Hepatobiliary/pancreatic source</td>
<td></td>
</tr>
<tr>
<td>Secondary peritonitis/abscess, panceatits/cholangitis</td>
<td>52</td>
</tr>
<tr>
<td>Primary peritonitis</td>
<td>8</td>
</tr>
<tr>
<td>Mortality (100 days)</td>
<td>28%</td>
</tr>
<tr>
<td>Bacterial co-infection</td>
<td>67%</td>
</tr>
<tr>
<td>Candidemia</td>
<td>6%</td>
</tr>
</tbody>
</table>
Unmet Needs

✓ Can we detect invasive candidiasis in the ICU earlier?
Determinants for success of Micafungin in ICU patients with Sepsis, Organ failure, and Candida colonization

<table>
<thead>
<tr>
<th></th>
<th>Micafungin Survived at Day 28, No.</th>
<th>Placebo Survived at Day 28, No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>90</td>
<td>128</td>
<td>1.04 (0.64-1.67)</td>
<td>.88</td>
</tr>
<tr>
<td>SOFA score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 8</td>
<td>53</td>
<td>66</td>
<td>0.79 (0.32-1.96)</td>
<td>.62</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>37</td>
<td>62</td>
<td>1.28 (0.71-2.27)</td>
<td>.42</td>
</tr>
<tr>
<td>Admission category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>23</td>
<td>34</td>
<td>0.97 (0.36-2.63)</td>
<td>.96</td>
</tr>
<tr>
<td>Medical</td>
<td>67</td>
<td>94</td>
<td>1.23 (0.69-2.22)</td>
<td>.48</td>
</tr>
<tr>
<td>Colonization index ≥ 0.5a</td>
<td>70</td>
<td>101</td>
<td>0.93 (0.54-1.59)</td>
<td>.78</td>
</tr>
<tr>
<td>Corrected colonization index ≥ 0.4b</td>
<td>54</td>
<td>76</td>
<td>56</td>
<td>80</td>
</tr>
<tr>
<td>Candida score ≥ 3</td>
<td>66</td>
<td>96</td>
<td>0.95 (0.55-1.67)</td>
<td>.87</td>
</tr>
<tr>
<td>(1-3)-β-D-glucan, pg/mLc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 250</td>
<td>14</td>
<td>21</td>
<td>0.96 (0.27-3.33)</td>
<td>.95</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>61</td>
<td>91</td>
<td>0.98 (0.55-1.75)</td>
<td>.96</td>
</tr>
<tr>
<td>≤ 80</td>
<td>29</td>
<td>37</td>
<td>0.85 (0.27-2.63)</td>
<td>.78</td>
</tr>
</tbody>
</table>
**T2 Candida in ICU patients at high risk of candidemia / invasive candidiasis in Europe**

<table>
<thead>
<tr>
<th>Candidiasis*</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven</td>
<td>11  (9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- BC</td>
<td>5/11</td>
<td>45%</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>- T2</td>
<td>6/11</td>
<td>55%</td>
<td>93%</td>
<td>50%</td>
<td>96%</td>
</tr>
<tr>
<td>- Mannan Ag</td>
<td>4/11</td>
<td>36%</td>
<td>94%</td>
<td>36%</td>
<td>94%</td>
</tr>
<tr>
<td>Likely</td>
<td>6 (5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven + Likely</td>
<td>17 (14%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- BC</td>
<td>5/17</td>
<td>29%</td>
<td>100%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>- T2</td>
<td>10/17</td>
<td>59%</td>
<td>96%</td>
<td>83%</td>
<td>94%</td>
</tr>
<tr>
<td>- Mannan Ag</td>
<td>7/17</td>
<td>41%</td>
<td>96%</td>
<td>64%</td>
<td>91%</td>
</tr>
<tr>
<td>Possible</td>
<td>11 (9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prov+Poss+Likely</td>
<td>28 (22%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- BC</td>
<td>5/28</td>
<td>18%</td>
<td>100%</td>
<td>100%</td>
<td>81%</td>
</tr>
<tr>
<td>- T2</td>
<td>11/28</td>
<td>39%</td>
<td>97%</td>
<td>92%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Proven: +ve BC or normally sterile site  
Likely: Colonization ≥2 sites AND either SIRS or Mannan Ag>250  
Possible: Colonization ≥2 sites +MAg>125 OR Mag≥250 OR Colonized + SIRS despite ABx  

Arendrup et al, Open Forum Infect Dis 2019

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**Initiation of antifungal treatment (prophylactic/empiric)**  
**OR**  
**T>38°C despite 3 days of Broad-spectrum Abx**  
**AND ≥2 risk factors:**  
- Abdominal surgery  
- Secondary peritonitis  
- Central venous catheter  
- TPN  
- Hemodialysis  
- Steroids/immunosuppressants  
- Liver transplant  

- False positives?  
  3 putative FP in this study  
- Sensitivity better than BC but underwhelming (with current gold standard)
Fungal Immunogenetics for Personalized Therapy

Host susceptibility to candidiasis in an ICU cohort

19-fold increased risk of developing candidemia in individuals carrying multiple specific polymorphisms
Unmet Needs

✓ Can we cover the emerging spectrum of *Candida* species?
Changing epidemiology of invasive candidiasis

- Changing species distribution
- Emerging *C. auris*
- Resistance to antifungal drugs
Distribution of *Candida* species according to prophylaxis used

### A Distribution Based on Duration of Prophylaxis

- **No Antifungal Prophylaxis**
  - *C. albicans*
  - *C. dubliniensis*
  - *C. tropicalis*
  - *C. glabrata*
  - *C. krusei*
  - *S. cerevisiae*
  - *C. parapsilosis*
  - Other candida species
  - Other fungi

- **Prophylaxis <7 Days**
  - *C. albicans*
  - *C. parapsilosis*
  - *C. glabrata*
  - *C. krusei*

- **Prophylaxis >7 Days**
  - *C. krusei*
  - *C. glabrata*

### B Distribution Based on Antifungal Agent Used for Prophylaxis

- **No Antifungal Prophylaxis**
  - *C. albicans*
  - *C. tropicalis*
  - *C. glabrata*
  - *C. krusei*
  - *C. parapsilosis*

- **Fluconazole Prophylaxis**
  - *C. glabrata*

- **Caspofungin Prophylaxis**
  - *C. parapsilosis*
  - *C. glabrata*
Unmet Needs

✓ Can we select the most effective initial antifungal drug?
## Treatment for candidemia

### IDSA 2016

<table>
<thead>
<tr>
<th>Compound</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anidulafungin 200→100 mg</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Caspofungin 70→50 mg</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Micafungin 100 mg</td>
<td>Strong</td>
<td>High</td>
</tr>
</tbody>
</table>

### ESCMID 2012

<table>
<thead>
<tr>
<th>Compound</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin 200→100 mg</td>
<td>A I</td>
<td>I</td>
</tr>
<tr>
<td>Caspofungin 70→50 mg</td>
<td>A I</td>
<td>I</td>
</tr>
<tr>
<td>Micafungin 100 mg</td>
<td>A I</td>
<td>I</td>
</tr>
<tr>
<td>L-Amphotericin B 3 mg/kg</td>
<td>B I</td>
<td>I</td>
</tr>
<tr>
<td>Voriconazole 6→3 mg/kg bid</td>
<td>B I</td>
<td>I</td>
</tr>
<tr>
<td>Fluconazole 400→800 mg</td>
<td>C I</td>
<td>I</td>
</tr>
</tbody>
</table>

Echinocandin superior to azole for candidemia

Success (%)

- Anidulafungin
- Fluconazole
- Caspofungin
- Isavuconazole

Δ15.4%
p=0.009

Δ10.8%
P<0.05

Reboli et al. 2007

Kullberg et al. 2019

75.6%
60.2%
71.1%
60.3%

N=127
N=118
N=201
N=199

Case Study (2)

- A 62 year-old woman underwent abdominal surgery for a cholangiocarcinoma

- Post-operative ICU stay, fever 39.6°C
- Piperacillin-tazobactam and vancomycin

- Rule out suture leak

- Repeat abdominal CT negative
- Blood cultures negative
- T2 Candida positive: *C. krusei/glabrata*
- Started on caspofungin

- Afebrile, clinically stable
- Ready for discharge – which antifungal – if any?
Unmet Needs

✓ Do we know the optimal duration of treatment?
Early echinocandin to azole stepdown in candidemia patients

<table>
<thead>
<tr>
<th>All pts started on iv anidulafungin</th>
<th>All patients</th>
<th>Early (≥ Day 5) switch population</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (N) [95% CI]</td>
<td>% (N) [95% CI]</td>
<td></td>
</tr>
<tr>
<td>MITT population (N)</td>
<td>250</td>
<td>102</td>
</tr>
<tr>
<td>Global success at EOT</td>
<td>68% (170/250) [62.2–73.8]</td>
<td>79% (81/102) [71.6–87.3]</td>
</tr>
<tr>
<td>Mortality (ITT population)</td>
<td>23% (65/282)</td>
<td>14% (14/102)</td>
</tr>
<tr>
<td>Success at end of iv therapy</td>
<td>83% (208/250) [78.6–87.8]</td>
<td>95% (97/102) [90.3–99.3]</td>
</tr>
</tbody>
</table>

Current practice:
✓ Start all patients on echinocandin
✓ Continue echinocandin until stabilization
✓ DO switch early after stabilization and negative follow-up blood culture, if azole-susceptible

Unknowns:
✓ What if ready for early discharge / azole-resistant / azole drug-drug interactions?
Summary thoughts – Unmet needs

- Changing epidemiology / species distribution / resistance / emerging species at least partly under pressure of prophylactic/empiric antifungal use

- Non-culture *Candida* detection and biomarker studies mostly underwhelming but nevertheless the way to go

- Need to better identify patients at risk for candidemia/invasive candidiasis (with conventional methods or immunogenetics)

- Supporting data on superiority of echinocandins for candidemia/invasive candidiasis

- Rapid step down to azoles in stabilized patients is feasible, but limited by susceptibility and drug-drug interactions

- Need for additional iv/oral antifungal classes with broad spectrum, deep tissue penetration for in/outpatient use

Thank you
Rezafungin for Treatment of Invasive Candidiasis

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Division of Infectious Diseases
Department of Internal Medicine
Department of Medical Microbiology and Immunology
University of California-Davis Medical Center
Disclosures / Acknowledgments

• **G. R. Thompson**: Cidara Therapeutics (investigator, research support); Mayne (investigator, research support); Astellas (consultant, investigator, consulting fee, research support); Scynexis (investigator, research support); Vical (consultant, consulting fee)

• Editorial support was provided by T. Chung (Scribant Medical) and funded by Cidara Therapeutics.
STRIVE Phase 2 Trial of Rezafungin Treatment
Documented Candidemia & Invasive Candidiasis

Objectives

To establish:

- Safety and tolerability
- Clinical and mycological efficacy across timepoints
- Efficacy vs caspofungin
- Dosing regimen for Phase 3
## Demographics and Baseline Characteristics
### ITT Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rezafungin 400 mg Wk 1 / 400 mg QWk N=81</th>
<th>Rezafungin 400 mg Wk1 / 200 mg QWk N=57</th>
<th>Caspofungin 70 mg Day 1 / 50 mg QD N=69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean [Range]</td>
<td>60 y [24-88]</td>
<td>60 y [24-91]</td>
<td>59 y [24-93]</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidemia</td>
<td>76.5%</td>
<td>80.7%</td>
<td>81.2%</td>
</tr>
<tr>
<td>IC</td>
<td>23.5%</td>
<td>19.3%</td>
<td>18.8%</td>
</tr>
<tr>
<td>APACHE IIa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>28.4%</td>
<td>26.3%</td>
<td>24.6%</td>
</tr>
<tr>
<td>10-19</td>
<td>48.1%</td>
<td>45.6%</td>
<td>53.6%</td>
</tr>
<tr>
<td>≥20</td>
<td>21.0%</td>
<td>24.6%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Mean score</td>
<td>13.4</td>
<td>14.1</td>
<td>14.0</td>
</tr>
</tbody>
</table>

Subjects with scores not calculated/missing not shown.
**Candida Species at Enrollment**

**mITT Population**

- **C. albicans**: 46%
- **C. glabrata**: 19%
- **C. tropicalis**: 11%
- **C. parapsilosis**: 14%
- **C. dubliniensis**: 3%
- **C. krusei**: 3%
- **Other***...: ~54% of baseline isolates

* C. fermentati, C. intermedia, C. kefyr, C. metapsilosis, C. rugosa, C. utilis (n=1 each), and C. guilliermondii (n=2)

Total number of isolates: 196
# Primary Outcome: Overall Response

## Day 14 – mITT Population

<table>
<thead>
<tr>
<th>Overall Response n (%)</th>
<th>Rezafungin 400 mg Wk 1 / 400 mg QWk N=76</th>
<th>Rezafungin 400 mg Wk1 / 200 mg QWk N=46</th>
<th>Caspofungin 70 mg Day 1 / 50 mg QD N=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>46 (60.5)</td>
<td>35 (76.1)</td>
<td>41 (67.2)</td>
</tr>
<tr>
<td>Failure</td>
<td>20 (26.3)</td>
<td>8 (17.4)</td>
<td>17 (27.9)</td>
</tr>
</tbody>
</table>

Overall Response = mycological success AND resolution of signs attributable to candidemia/IC

Indeterminate outcomes (those unable to be assessed due to missing data point[s]) not shown. mITT = microbiological intent-to-treat (all who received study drug and had documented *Candida* infection).
Summary of Rezafungin Efficacy Results

**mITT Population**

1. **Overall Response D14**
   - Rezafungin 400mg/400mg QWk (N=76): 60.5%
   - Rezafungin 400mg/200mg QWk (N=46): 76.1%
   - Caspofungin 70mg/50mg QD (N=61): 67.2%

2. **PI Assessed Clin Response D14**
   - Rezafungin 400mg/400mg QWk (N=76): 69.7%
   - Rezafungin 400mg/200mg QWk (N=46): 80.4%
   - Caspofungin 70mg/50mg QD (N=61): 70.5%

3. **All-Cause Mortality D30**
   - Rezafungin 400mg/400mg QWk (N=76): 15.8%
   - Rezafungin 400mg/200mg QWk (N=46): 4.3%
   - Caspofungin 70mg/50mg QD (N=61): 13.1%
PI Assessment of Clinical Response by *Candida* spp.

Day 14 – mITT Population

<table>
<thead>
<tr>
<th>Strain</th>
<th>Rezafungin 400mg/400mg QWk (N=76)</th>
<th>Rezafungin 400mg/200mg QWk (N=46)</th>
<th>Caspofungin 70mg/50mg QD (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>57.9</td>
<td>84.2</td>
<td>71.4</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>92.3</td>
<td>85.7</td>
<td>73.5</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>80.0</td>
<td>85.7</td>
<td>63.6</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>55.6</td>
<td>71.4</td>
<td>50.0</td>
</tr>
</tbody>
</table>

No. of cases:
- *C. albicans*: 38, 19, 34
- *C. glabrata*: 13, 14, 10
- *C. parapsilosis*: 10, 7, 11
- *C. tropicalis*: 9, 7, 6
## Overall Response
### Day 5 – mITT Population

<table>
<thead>
<tr>
<th>Overall Response n (%)</th>
<th>Rezafungin 400 mg Wk1/400 mg QWk N=76</th>
<th>Rezafungin 400 mg Wk1/200 mg QWk N=46</th>
<th>All Rezafungin (Pooled) N=122</th>
<th>Caspofungin 70 mg Day 1 50 mg QD N=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>42 (55.3)</td>
<td>34 (73.9)</td>
<td>76 (62.3)</td>
<td>34 (55.7)</td>
</tr>
<tr>
<td>Failure</td>
<td>24 (31.6)</td>
<td>10 (21.7)</td>
<td>34 (27.9)</td>
<td>24 (39.3)</td>
</tr>
</tbody>
</table>

Day 5 outcomes reflect the **initial** dose of 400 mg in both RZF-treated arms

Indeterminate outcomes (those unable to be assessed due to missing data point[s]) not shown.
mITT = microbiological intent-to-treat (all who received study drug and had documented *Candida* infection).
# Mycological Response

**Day 14 – mITT Population (Patients with Candidemia Only)**

Indeterminate outcomes (those unable to be assessed due to missing data point[s]) not shown.

mITT = microbiological intent-to-treat (all who received study drug and had documented *Candida* infection).

<table>
<thead>
<tr>
<th>Mycological Response</th>
<th>Rezafungin 400 mg Wk 1 / 400 mg QWk N=57</th>
<th>Rezafungin 400 mg Wk1 / 200 mg QWk N=36</th>
<th>Caspofungin 70 mg Day 1 / 50 mg QD N=48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>38 (66.7)</td>
<td>25 (69.4)</td>
<td>32 (66.7)</td>
</tr>
<tr>
<td>Failure</td>
<td>14 (24.6)</td>
<td>8 (22.2)</td>
<td>14 (29.2)</td>
</tr>
</tbody>
</table>
# Summary of Adverse Events
## Safety Population

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rezafungin 400 mg Wk1/400 mg QWk N=81</th>
<th>Rezafungin 400 mg Wk1/200 mg QWk N=53</th>
<th>Rezafungin (Pooled) N=134</th>
<th>Caspofungin 70 mg Day 1 50 mg QD N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 TEAE</td>
<td>71 (87.7)</td>
<td>49 (92.5)</td>
<td>120 (89.6)</td>
<td>55 (80.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>29 (35.8)</td>
<td>17 (32.1)</td>
<td>46 (34.3)</td>
<td>26 (38.2)</td>
</tr>
<tr>
<td>Study drug–related</td>
<td>7 (8.6)</td>
<td>6 (11.3)</td>
<td>13 (9.7)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>TEAE leading to study D/C</td>
<td>6 (7.4)</td>
<td>1 (1.9)</td>
<td>7 (5.2)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>35 (43.2)</td>
<td>28 (52.8)</td>
<td>63 (47.0)</td>
<td>29 (42.6)</td>
</tr>
<tr>
<td>Study drug–related</td>
<td>1 (1.2)</td>
<td>1 (1.9)</td>
<td>2 (1.5)</td>
<td>2 (2.9)</td>
</tr>
</tbody>
</table>

D/C=discontinuation; TEAE (treatment-emergent adverse event)=AE that occurs after first dose of study drug is administered.
# Treatment-Emergent Adverse Events (≥10%)

## Safety Population

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Rezafungin 400 mg Wk1/400 mg QWk N=81</th>
<th>Rezafungin 400 mg Wk1/200 mg QWk N=53</th>
<th>Rezafungin (Pooled) N=134</th>
<th>Caspofungin 70 mg Day 1/ 50 mg QD N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>13 (16.0)</td>
<td>9 (17.0)</td>
<td>22 (16.4)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (8.6)</td>
<td>11 (20.8)</td>
<td>18 (13.4)</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (7.4)</td>
<td>8 (15.1)</td>
<td>14 (10.4)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (11.1)</td>
<td>4 (7.5)</td>
<td>13 (9.7)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (7.4)</td>
<td>7 (13.2)</td>
<td>13 (9.7)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (4.9)</td>
<td>8 (15.1)</td>
<td>12 (9.0)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5 (6.2)</td>
<td>6 (11.3)</td>
<td>11 (8.2)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>9 (11.1)</td>
<td>1 (1.9)</td>
<td>10 (7.5)</td>
<td>3 (4.4)</td>
</tr>
</tbody>
</table>
Ongoing Phase 3 ReSTORE Trial
Rezafungin Treatment of Candidemia & Invasive Candidiasis
Summary

- STRIVE findings which established rezafungin
  - Clinical safety and tolerability
  - Efficacy (clinical and mycological) across time points and versus caspofungin
  - Once weekly dosing of 400 mg Week 1 / 200 mg Qweek

- Results of STRIVE support ongoing phase 3 development of rezafungin for treatment of candidemia and invasive candidiasis and prophylaxis of IFI

- Stop by poster #436 on Sunday for more details on STRIVE
PREVENTION OF INVASIVE FUNGAL INFECTIONS IN VULNERABLE HOSTS

KIEREN A. MARR MD, MBA

PROFESSOR OF MEDICINE, JOHNS HOPKINS SCHOOL OF MEDICINE
DIRECTOR, TRANSPLANT AND ONCOLOGY INFECTIOUS DISEASES
VICE CHAIR OF MEDICINE FOR INNOVATION IN HEALTHCARE IMPLEMENTATION
COMMERCIAL ACTIVITY DISCLOSURE

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  • AMPLYX, CHIMERIX, CIDARA, MERCK

• EDITORIAL ROLES
  • UPTODATE

• LICENSED TECHNOLOGY / OWNERSHIP
  • MYCOMED TECHNOLOGIES
OUTLINE

• PROPHYLAXIS – FOUNDATION AND HISTORY

• REAL-LIFE EPIDEMIOLOGY

• TRIAL DESIGN
  • RESPECT: 1-DRUG PREVENTION WITH REZAFUNGIN

• FUTURE POTENTIALS: UNMET NEEDS IN HEMATOLOGIC MALIGNANCIES
Efficacy and Safety of Fluconazole Prophylaxis for Fungal Infections after Marrow Transplantation—A Prospective, Randomized, Double-Blind Study

Monica A. Slavin, Barbara Osborne, Robyn Adams, Marcia J. Levenstein, H. Gary Schoch, Allen R. Feldman, Joel D. Meyers,* and Raleigh A. Bowden

Fred Hutchinson Cancer Research Center, Seattle, Washington; New York, New York; Royal Melbourne Hospital, Melbourne, Australia

Intravenous and Oral Itraconazole versus Intravenous and Oral Fluconazole for Long-Term Antifungal Prophylaxis in Allogeneic Hematopoietic Stem-Cell Transplant Recipients

A Multicenter, Randomized Trial

Drew J. Winston, MD; Richard T. Maziarz, MD; Pranatharthi H. Chandrasekar, MD; Hillard M. Lazarus, MD; Mitchell Goldman, MD; Jeffrey L. Blumer, PhD; Gerhard J. Letz, PhD; and Mary C. Terni, MD

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

Oliver A. Corney, MD; Johan Maertens, MD; Drew J. Winston, MD; John Perfect, MD; Andrew J. Ullmann, MD; Thomas J. Walsh, MD; David Helgott, MD; Jerzy Holowiecki, MD; Dick Stockberg, MD; Yeow-Tee Goh, MD; Mario Petriani, MD; Cathy Hardal, MD; Ramachandran Suresh, PhD; and David Angulo-Gonzalez, MD.*

Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allogeneic hematopoietic cell transplantation (HCT)

AZOLE PROPHYLAXIS - BMT

• **FLUCONAZOLE PREVENTS CANDIDIASIS**
  • NEW COMPARATOR FOR MOLD-ACTIVE AZOLES

• **TWO RANDOMIZED TRIALS EVALUATING ITROCONAZOLE SOLUTION IN BMT PATIENTS**
  • BOTH
    • DECREASED INVASIVE ASPERGILLOSIS IN ITROCONAZOLE ARM
    • TREND TO WORSE SURVIVAL IN ITROCONAZOLE ARM

• **TOXICITIES OF DRUG**
  • GI TRACT TOXICITIES
  • DRUG INTERACTIONS

Is decreased IA “caused” by informative censoring?

Marr et al, Blood 2004 103(4): 1527-33
POSACONAZOLE

• POSACONAZOLE VS. FLUCONAZOLE (N=600 PATIENTS)
  • DRUG WITH DIAGNOSIS OF GVHD
• APPROVED FOR PROPHYLAXIS IN BMT & AML/MDS

Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation


600 patients enrolled in NHLBI BMT CTN protocol 0101

- Standard risk allo HCT
- Mould-active prophylaxis: voriconazole
- 1º endpoint: fungal free survival
- Day 120-180
- Fluconazole + targeted therapy (GM EIA)
## Ullmann trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>POS n (%)</th>
<th>FLU n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Period (120 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16 (5)</td>
<td>27 (9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>7 (2)</td>
<td>21 (7)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

N=600 total patients (301 POS group, 299 FLU group).

## BMT CTN trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VORI n (%)</th>
<th>FLU n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Period (180 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14 (4.6)</td>
<td>24 (8.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>9 (3.0)</td>
<td>17 (5.8)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

N=600 total patients (305 VORI group, 295 FLU group).

Risk reduction 0.037 vs. 0.04
ISAVUCONAZOLE

• APPROVED FOR THERAPY OF INVASIVE ASPERGILLIOSIS

• OBSERVATIONS: USED FREQUENTLY, ESPECIALLY WITH LIVER TOXICITIES, PEOPLE WITH LONG QT

• REPORTS OF FREQUENT BREAKTHROUGH

• REASONS UNKNOWN
  • BIAS?
  • ANTIFUNGAL LEVELS? (TDM)
  • RESISTANCE? AT LEAST ONE CASE OF TR34-L98H RESISTANT A. FUMIGATUS BREAKTHROUGH REPORTED

REAL-WORLD EPIDEMIOLOGY

- CIBMTR STUDY – ACUTE LEUKEMIA WITH ALTERNATIVE DONORS: MATCHED, UNRELATED DONORS (MUD), MISMATCHED, UNRELATED DONORS (MMUD) AND CORD BLOOD (UCB)

- INCIDENCE OF IFI REMAINS HIGH

- “PREVENTABLE IFI”:
  - BOTH IA AND CANDIDIASIS
REAL – WORLD RECURRENT INFECTIONS

• INFECTIOUS MORBIDITY BETTER APPRECIATED AS CUMULATIVE, RECURRENT EVENTS

• SWIMMER-LANE PLOTS: PROVIDE CONTROL FOR INFORMATIVE CENSORING AND DEMONSTRATES ‘REAL-LIFE’ FAILURE

• A LOT OF MORBIDITY DESPITE EFFECTIVE PREVENTION ALGORITHMS

• HETEROGENEITY

• IFI OCCUR LARGELY BEFORE DEATH
SUCCESS = BALANCE

Benefits
- Prevent IFI
- morbidity
- mortality
- Secondary

Risks
- Toxicities
- Drug interactions
- Drug resistance
- Costs

Each drug has different benefits and risks when utilized in different settings
PNEUMOCYSTIS INFECTION
FRENCH BMT OBSERVATION

- ONLY 45% OF 139 CONSECUTIVE PATIENTS RECEIVED FULL COURSE OF TMP/SMX
  - 60 PATIENTS SWITCHED DUE TO SIDE EFFECT
  - 18 CONFIRMED PCP CASES (12.9% INCIDENCE)
- FREQUENT FAILURE DUE TO POOR TOLERABILITY IN REAL-WORLD

Fig. 1 Flow chart of pneumocystis prophylaxis in 139 consecutive allogeneic HCT recipients

Redjoul et al. BMT 2019 54: 1082-88
REZAFUNGIN
ANTIFUNGAL PROPHYLAXIS: RATIONALE

• ONCE – WEEKLY INFUSION
• NO CYTOCHROME P450 INTERACTIONS
• PRECLINICAL, CLINICAL ACTIVITY AGAINST CANDIDA SPP.
• PRECLINICAL ACTIVITY AGAINST ASPERGILLUS & PCP
Rezafungin

Aspergillosis & PCP models

Aspergillosis in neutropenic mice:
Equivalent survival in humanized doses relative to AmB

PCP in neutropenic and steroid-suppressed mice:
Equivalent reduction in cysts and trophic forms relative to TMP/SMX

Log$_{10}$ mean nuclei and asci counts after 42 days of study drug administration.

10 mg/kg ≈ human dose of 200mg
20 mg/kg ≈ human dose of 400mg

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RESPECT TRIAL
ANTIFUNGAL PROPHYLAXIS IN BMT

• TO START Q1 2020 IN EUROPE

• RANDOMIZED, DOUBLE-BLIND COMPARISON OF ONCE WEEKLY REZAFUNGIN VS. STANDARD ANTIFUNGAL PROPHYLAXIS (AZOLE + TMP-SMX) AFTER ALLOBMT

• DESIGN (462, 2:1 RANDOMIZATION)
  • STANDARD-RISK ALLOGENEIC BMT (NO CBT, AML NOT IN MORPHOLOGIC REMISSION, RECENT IFI)
  • 90 DAYS REZA VS. CURRENT STANDARD (FLUCONAZOLE WITH POSA FOR GVHD & TMP/SMX)
  • POWERED TO MEASURE NON-INFERIORITY OF FUNGAL – FREE SURVIVAL & SUPERIORITY OF PROPHYLAXIS SUCCESS
RESPECT PHASE 3 TRIAL

Rezafungin Arm (n=300)

Week 1 2 3 4 5 12 13 17
Rezafungin
Azole placebo
Bactrim placebo

Day 1

1° Endpoint: Fungal Free Survival at Day 90
Follow up

Comparator Arm (n=150)

Week 1 2 3 4 5 12 13 17
Rezafungin Placebo
Azole*
Bactrim

Day 1

*Fluconazole to start in all patients. Posaconazole optional in patients who develop GVHD per label.
FUTURE APPLICATIONS?
UNMET NEEDS IN HEMATOLOGY

- INFECTIOUS RISKS POORLY DESCRIBED IN CLINICAL DEVELOPMENT
- EXPERIENCE UNDERLINING COMPLEX SECONDARY RISKS FOR IFI IN SEVERAL DRUGS
- MANY CONTRAINDICATIONS TO AZOLES DUE TO CYTOCHROME P450 INTERACTIONS

New chemotherapeutic agents already in use or coming in Hematology

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| 1. FLT3-inhibitors (Quizartinib, Midostaurin, Sorafenib) | 1. Monoclonal antibodies
| 2. Monoclonal antibodies anti-CD33 (Gentuzumab) |   a. anti-CD19 (Blinatumuzumab)
| 3. Arsenic Trioxide |   b. anti -CD22 (Inotuzumab)
| 4. IDH1-2 inhibitors | 2. TK inhibitors (Imatinib, Nilotinib, Dasatinib, Ponatinib)
| 5. Combined liposomal cytarabine and daublastine (CTX1) | Multiple Myeloma
| | 1. IMIDS (Talidomide, Lenalidomide Pomalidomide)
| | 2. Proteosome inhibitors (Bortezomib, Carfizomib)
| | 3. Monoclonal antibodies
| |   a. anti-CD38 (Daratumumab)
| |   b. anti-CD319 (Elotuzumab)
| Lymphomas (low and high grade) | CLL
| 1. BTK-inhibitors (Ibrutinib) | 1. BTK-inhibitors (Ibrutinib)
| 3. PI3Kδ signaling- inhibitor (Idelalisib) | 3. PI3Kδ signaling- inhibitor (Idelalisib)

Hodgkin’s Lymphoma

1. Monoclonal antibodies anti-CD30 (Brentuximab)
2. IgG4 anti-PD-1 (Nivolumab)

Slide: L. Pagano
IFI RISKS ARE COMPLEX AND SOMETIMES UNEXPECTED

• RISKS REPRESENT
  • CUMULATIVE FUNCTION OF HOST RISKS (EX. AGE, LUNG DISEASE), UNDERLYING DISEASE, PRIOR THERAPIES
  • MANY DRUGS (EX. CHECKPOINT INHIBITORS) CAUSE INFLAMMATORY SYNDROMES THAT REQUIRE SECONDARY IMMUNOSUPPRESSION
    • EXAMPLE: IFI AFTER STEROIDS GIVEN FOR PNEUMONITIS, COLITIS
  • NON-SPECIFIC EFFECTS OF ‘TARGETED’ DRUGS
TYROSINE KINASE INHIBITORS

• DRUGS TARGET B CELL RECEPTOR, INHIBIT ACTIVATION AT DIFFERENT SIGNALING TARGETS. USED FOR CLL, LYMPHOMAS

• IFI RISKS COMPLICATED. EXAMPLE IBRUTINIB (BRUTON’S TK INHIBITOR)
  • SINGLE-CENTER REVIEW: 11% INCIDENCE INFECTION
  • RELATIVELY HIGH INCIDENCE IFI (ESPECIALLY PCP & IA)
  • CNS ASPERGILLOSIS
  • MECHANISTIC STUDIES REVEAL INHIBITION OF MACROPHAGE AND PMN KILLING

• LIMITED OPTIONS FOR PROPHYLAXIS DRIVING EXPLORATION OF ALTERNATIVES

CONCLUSIONS

• LONG HISTORY OF STUDIES IN BMT DEMONSTRATE UTILITY OF ANTI-FUNGAL PROPHYLAXIS IN TRIALS
  • ANTI-CANDIDA, ASPERGILLUS AND PJP

• REAL-LIFE OUTCOMES COMPLICATED BY INABILITY TO TAKE PREVENTATIVE DRUGS FOR A LONG PERIOD OF TIME (DRUG INTERACTIONS, TOXICITIES)

• NEW STUDY TO START NEXT YEAR:
  • REZAFUNGIN 1-DRUG PROPHYLAXIS VS. STANDARD APPROACH
  • DESIGN CONSIDERS LESSONS LEARNED

• EVOLVING COMPLEX FIELD WITH UNMET NEEDS IN OTHER VULNERABLE HOSTS, ESPECIALLY WITH TARGETED BIOLOGICS
THANK YOU