Design and Conduct of Clinical Trials for Newer Antifungal Agents

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Challenges common to all AF clinical trials

• With the exception of invasive candidiasis and cryptococcosis (in lower income countries), these are relatively rare infections, enrollment tends to be very slow.

• Delay in diagnosis due to insensitive culture methods; limited availability of rapid, sensitive and specific non-culture based diagnostics (possible exception of IMMY’s LFA CrAg)

• Determination of AFR is also slow and susceptibility breakpoints not established for each organism/antifungal agent

• Traditional, RCT/DB trials are only applicable to candidiasis, aspergillosis, and cryptococcosis

• The study of antifungal resistant fungal infections is even more challenging
Invasive Candidiasis

• Development of AFR an emerging problem for all Candida species, but especially *C. glabrata*

• For most sites, AFR *Candida* constitute only about 5-25% of all isolates

• For most recent IC trials, enrollment success is approximately 1:10 pts with IC. Most common exclusions are: 1. too much prior AF therapy, 2. pt is too ill, 3. contraindicated drugs, 4. concomitant illness

• ‘Global response’ includes clinical, mycologic and mortality. Clinical endpoints are ‘soft’ (e.g., fever, local symptoms), whereas mycologic and survival endpoints are ‘hard’.

• How to incorporate T2MR, Candida PCR (Septifast®), β-D glucan, etc into eligibility criteria
The last of the candidemia mega-trials? Unlikely.

Isavuconazole Versus Caspofungin in the Treatment of Candidemia and Other Invasive Candida Infections: The ACTIVE Trial

Bart Jan Kullberg, Claudio Viscoli, Peter G Pappas, Jose Vazquez, Luis Ostrosky-Zeichner, Coleman Rotstein, Jack D Sobel, Raoul Herbrecht, Galia Rahav, Sutep Jaruratanasirikul, Ploenchlan Chetchotisank, Eric Van Wijngaerden, Jan De Waele, Christopher Lademacher, Marc Engelhardt, Laura Kovanda, Rodney Croos-Dabrera, Christine Fredericks, George R Thompson

**Table 3.** Response to treatment and all-cause mortality in the mITT population

<table>
<thead>
<tr>
<th>mITT Population</th>
<th>Isavuconazole (n=199)</th>
<th>Caspofungin (n=201)</th>
<th>Adjusted Difference$^1$ (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Response rates, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Overall response at EOivT</td>
<td>120 (60.3)</td>
<td>143 (71.1)</td>
<td>−10.8 (−19.9, −1.8)</td>
</tr>
<tr>
<td>Clinical response$^2$</td>
<td>152 (76.4)</td>
<td>169 (84.1)</td>
<td>−8.2 (−15.4, −0.9)</td>
</tr>
<tr>
<td>Microbiological response</td>
<td>141 (70.9)</td>
<td>172 (85.6)</td>
<td>−14.9 (−22.7, −7.0)</td>
</tr>
<tr>
<td>Overall response at EOT</td>
<td>122 (61.3)</td>
<td>145 (72.1)</td>
<td>−10.9 (−19.9, −1.9)</td>
</tr>
<tr>
<td>Overall response at 2 weeks after EOT</td>
<td>109 (54.8)</td>
<td>115 (57.2)</td>
<td>−2.9 (−12.4, 6.5)</td>
</tr>
<tr>
<td>Overall response at 6 weeks after EOT</td>
<td>86 (43.2)</td>
<td>97 (48.3)</td>
<td>−5.4 (−15.5, 4.2)</td>
</tr>
</tbody>
</table>

| All-cause Mortality, n (%)      |                       |                     |                                  |
| Day 14 all-cause mortality     | 29 (14.6)             | 25 (12.4)           | 2.5 (−3.8, 8.9)                  |
| Day 56 all-cause mortality     | 61 (30.7)             | 60 (29.9)           | 1.4 (−7.1, 10.0)                 |

Clin Infect Dis 2018 (in press)
A traditional approach: rezafungin (CD 101)

• Long-acting echinocandin (ECH) with little enhanced spectrum compared to existing ECH. Can be dosed once weekly.
• Initial Ph II study enrolled 92 evaluable pts, RCT, DB, dose ranging study comparing CD 101 to caspofungin followed by fluconazole.
Focus on AF-resistant *Candida* strains

Absent a rapid diagnostic for species and AF-resistance, clinical trial design will need to consider clinical and/or mycologic screening that will enrich for MDR Candida:

1. Population-based (eg, stem cell transplant recipients), SICU/MICU pts where AFT is widespread
2. Prior exposure to azoles/ECH
3. Breakthrough infections, persistent clinical/mycologic evidence of infection despite therapy
4. Recent epidemiologic factors (travel, chronic care facility, etc)
MSG 16 (Nature Study)

• Observational study of pts with candidemia and echinicandin failure
• Capture key demographic, treatment, outcome data
• Up to 120 pts to be enrolled in US and possibly Latin America
• Study initiation in fall 2018
• Ostrosky-Zeichner PI, Scynexis is sponsor
Ibrexafungerp (SCY 078)

- SCY 078 is an oral glucan-synthase inhibitor
- Ph II RCT (open-label) was conducted as a dose ranging step down trial for pts with IC who had successfully completed iv ECH
- Primary outcome was PK based, clinical outcome was secondary based on too few potential pts
- This trial struggled to enroll (27 pts, 22 ITT evaluable), original target 90 pts, adequate data to determine the optimal daily dose based on PK parameters
- This study was transitioned to a salvage study (FURI) targeting patients with drug-resistant Candida isolates, those failing or intolerant to conventional therapy.
- Traditional, large RCT candidemia study could be the next step vs a focus on AFR Candida isolates
Fosmangepix (APX001)

• Phase II, single arm open label trial of APX001 for subjects with candidemia, with focus on *C. glabrata* and other azole-resistant *Candida*

• Study now complete, enrollment 22

• International study involving approx 10 sites

• 18 months to complete enrollment

• ‘Success’ achieved in over 70%
Invasive Aspergillosis: Challenges

• IA occurs at about 1/10 frequency of IC
• Most cases are diagnosed as probable based on positive serum+/-BAL aspergillus galactomannan or PCR; cultures usually unavailable
• Protracted therapy (up to 12 weeks) sometimes required
• Underlying disease (e.g., recurrent leukemia, persistent neutropenia, progressive tumor) may have a significant impact on mortality
• Follow up mycologic studies, other than serum GM or PCR, are unusual, thus serial radiologic response is typically a surrogate of mycologic response
IA: Traditional approach

• Voriconazole vs posaconazole monotherapy for IA (completed, over 400 pts enrolled). **Study completed in its 7th year**

• **Combination antifungal therapy for invasive aspergillosis: a randomized trial.** Marr KA, et al Ann Intern Med. 2015 Jan 20;162(2):81-9. **This study required 4 years for completion**

IA: Upcoming Studies

• Amplyx: considering combination trial
• Scynexis: considering combination trial with an azole
• F2G (F901318): Phase IIb ongoing study, F901318 as Treatment of Invasive Fungal Infections Due to *Lomentospora Prolificans*, *Scedosporium Spp.*, *Aspergillus Spp.*, and Other Resistant Fungi in Patients Lacking Suitable Alternative Treatment Options. Primary or salvage therapy
• Proposed Phase III F2G vs LAmB for probable IA (in development)
Combination Therapy Studies: Cryptococcal Meningitis

• Complex design, requiring more pts than traditional non-inferiority studies
• Superiority generally needs to be demonstrated to justify a combination over mono therapy (why else would one choose to add a second agent?)
• Clinical/radiographic, toxicity, and mycologic measures important...meeting superiority criteria in all aspects is difficult. Most would emphasize clinical outcomes (survival) as pre-eminent
• Availability of a mycologic endpoint (CSF EFA) and the correlation of EFA with outcome facilitates conduct of study and reduces N
The Need for Better Fungal Diagnostics

- Culture-based methods are slow (days-weeks) and insensitive (50-70% for candidemia)
- Availability of NMR and PCR technology for early diagnosis from blood samples is a step forward, but many issues remain
- Molecular markers of resistance are essential if early treatment decisions are to be data driven.
- Biomarkers to assess response to therapy (eg, T2MR, PCR, GM, EFA)
- Improvement/development of clinical breakpoints for the more common fungal pathogens
- POC rapid diagnostics must be utilized to recruit subjects with probable IFI
The Future of Antifungal Clinical Trials

• The ‘standard model’ for RCTs targeting antifungal resistant organisms doesn’t really work well here for less common infections, numbers of potential pts is relatively small

• Protocol development targeting high-risk populations, enhanced enrollment using rapid molecular diagnostics are essential

• Clinical strategies utilizing an ‘enriched’ population (eg, targeting pts with candidemia who are receiving fluconazole to enhance number of pts with *C. glabrata*)

• Utilize the *global* population to achieve enrollment goals (eg, utilize sites in India and SE Asia to identify *C. auris* infections; Africa and SE Asia, LA for *Cryptococcus*, global community for IA and rare molds)