Design and Conduct of Clinical Trials for Newer Antifungal Agents

Peter G. Pappas, MD, FACP

William E. Dismukes Professor of Medicine

PI, Mycoses Study Group

Division of Infectious Diseases

University of Alabama at Birmingham

Disclosures

- Research grants: Cidara, Amplyx, Astellas, Merck, Scynexis, Gilead, IMMY
- Scientific advisor: Cidara, Amplyx, IMMY, Scynexis
- Speakers’ bureau: NA
- Equities: NA

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 [1], Claudio Viscoli [2 3], Peter G Pappas [4], Jose Vazquez [5], Luis Ostrosky-Zeichner [6], Coleman Rotstein [7], Jack D Sobel [8], Raoul Herbrecht [9], Galia Rahav [10], Sutep Jaruratanasirikul [11], Ploenchan Chetchotisakd [12], Eric Van Wijngaerden [13], Jan De Waele [14], Christopher Lademacher [15], Marc Engelhardt [16], Laura Kovanda [15], Rodney Croos-Dabrera [15], Christine Fredericks [15], George R Thompson [17]

Clin infect Dis 2019;68(12):1981-1989

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

mITT Population	Isavuconazole (n=199)	Caspofungin (n=201)	Adjusted Difference[1] (95% CI)
Response rates, n (%)			
Overall response at EOivT	120 (60.3)	143 (71.1)	−10.8 (−19.9, −1.8)
Clinical response[2]	152 (76.4)	169 (84.1)	−8.2 (−15.4, −0.9)
Microbiological response	141 (70.9)	172 (85.6)	−14.9 (−22.7, −7.0)
Overall response at EOT	122 (61.3)	145 (72.1)	−10.9 (−19.9, −1.9)
Overall response at 2 weeks after EOT	109 (54.8)	115 (57.2)	−2.9 (−12.4, 6.5)
Overall response at 6 weeks after EOT	86 (43.2)	97 (48.3)	−5.4 (−15.5, 4.2)
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**
- Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. **Maertens JA**, et al Lancet. 2016 Feb 20;387(10020):760-9. **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)