FINDINGS FROM: Pfaller MA et al. Effectiveness of anidulafungin in eradicating *Candida* species in invasive candidiasis. *Antimicrob Agents Chemother*. 2005;49:4795-4797.

Publication reprint available in this room.

INTRODUCTION[1]

- Pfaller and colleagues analyzed *Candida* isolates obtained in a previous study performed by Krause and colleagues for their susceptibility to anidulafungin. Pfaller and colleagues also compared the pathogen eradication rates obtained for different species and for different anidulafungin dosages

STUDY BACKGROUND

- *Candida* spp are the most common cause of systemic fungal infection[2] and are associated with the highest mortality among the 10 most common pathogens causing nosocomial bloodstream infection (BSI)[3]
- Non-*albicans* spp such as *C glabrata* and *C tropicalis* cause a significant proportion of *Candida* BSIs[4,5] and are associated with higher mortality rates compared with *C albicans*[3]
- The toxicity of polyenes and resistance to azoles have led to increased interest in alternative classes of antifungal agents[1]
- Anidulafungin is an echinocandin antifungal indicated for candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis). Anidulafungin has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida* and has not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group. Anidulafungin is active in vitro against many *Candida* spp[6,7]

STUDY METHODS

Design of Previous Study

- The phase 2 study was a randomized, open-label, noncomparative, dose-ranging trial of anidulafungin in 123 adults with invasive candidiasis, 94% of whom had candidemia[8]
- The patients were randomly assigned to anidulafungin 50, 75, or 100 mg/day following a loading dose that was double the daily maintenance dose[8]
- 120 patients, 40 in each treatment arm, received ≥1 dose of anidulafungin comprising the intent-to-treat population[8]
- Treatment continued for 2 weeks after resolution of infection (blood and tissue cultures negative or presumed to be negative if not obtainable), but for no longer than 42 days[8]
- Blood was cultured at baseline, periodically throughout treatment, at the follow-up visit (scheduled 2 weeks after the end of treatment or at the time of treatment failure), and as clinically indicated[1]
- Primary end point–global response (both clinical and microbiological response) at the follow-up visit in the evaluable (per protocol) population[8]
- Microbiological intent-to-treat population–116 patients who had confirmed *Candida* infection and received ≥1 dose of anidulafungin[8]
- Evaluable population–68 patients from the microbiological intent-to-treat population (18 in the 50-mg/day group, 26 in the 75-mg/day group, and 24 in the 100-mg/day group) who[8]:
  - Received ≥10 doses of anidulafungin or failed to respond to anidulafungin after ≥5 doses
    and
  - Had no protocol violations

Analysis of *Candida* Isolates[1]

- From the microbiological intent-to-treat population, there were 127 *Candida* isolates at baseline
- The isolates were sent to an academic medical center for definitive determination of species level and anidulafungin minimum inhibitory concentration (MIC)
- The Clinical and Laboratory Standards Institute broth microdilution method was used for MIC determinations
- The MIC end point used was complete inhibition after 48 hr of incubation, the standard at the time the study was initiated

Table 1. Distribution of baseline *Candida* spp and anidulafungin MICs

Species [no. of isolates (%)*]	n†	MIC‡ range	MIC_{50}§	MIC_{90}
C albicans [62 (49)]	59	0.03–4	0.12	0.25
C glabrata [36 (28)]	31	0.06–0.5	0.25	0.25
C parapsilosis [11 (9.5)]	11	4–8	4	8
C tropicalis [10 (8.6)]	7	0.12–2	0.5	

*All baseline isolates from the microbiological intent-to-treat population.
†Baseline isolates from the microbiological intent-to-treat population for which MICs were available.
‡MICs in µg/mL; 100% inhibition for study isolates.
§MICs at which 50% of the isolates tested were inhibited.

Adapted from Pfaller MA et al.[1]

STUDY RESULTS[1]

MICs

- Table 1 gives the distribution of *Candida* spp at baseline and the MICs
- The overall median MIC was 0.25 µg/mL
- Most MICs above 1 µg/mL were attributable to *C parapsilosis*

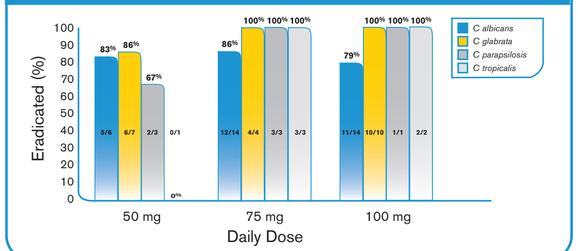
The recommended dose for anidulafungin in the treatment of candidemia and other *Candida* infections (intra-abdominal abscess and peritonitis) is a single 200-mg loading dose on Day 1, followed by a 100-mg daily dose thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive blood culture.

No correlation between in vitro activity (MIC) of anidulafungin and clinical outcome has been established.

Eradication Rates

- In the evaluable population there were 73 *Candida* isolates at baseline. Figure 1 shows the eradication rates of the most commonly isolated *Candida* spp in the evaluable population
- Overall, 61 of the 73 isolates (84%) were eradicated (or, in 1 patient with no follow-up culture, presumed to be eradicated), and 49 of these were documented by negative blood cultures
- Overall, 89% of isolates were eradicated in the 100 mg/day treatment arm
- Response to therapy was not related to anidulafungin MIC (Table 2)
  - 6 of the 7 *C parapsilosis* isolates, with MICs of 4 to 8 µg/mL, were eradicated from the 3 study arms

Figure 1. Eradication rates in the evaluable population



Adapted from Pfaller MA et al.[1]

Table 2. Response to therapy by MIC and daily dose of anidulafungin for baseline isolates of *Candida* spp

	No. of isolates tested (n) and % success (%S) by anidulafungin dose (mg/day)							
	50		75		100		All	
MIC (µg/mL)	n	%S	n	%S	n	%S	n	%S
0.03			1	0			1	0
0.06			2	100	2	100	4	100
0.12	3	66	7	71	7	100	17	82
0.25	10	70	8	88	13	77	31	77
0.5	1	100	1	100	1	0	3	66
1								
2			1	100	1	100	2	100
4	2	50	2	100	2	100	6	83
8	1	100					1	100
Unknown*	2	100	5	100	2	100	9	100

*MIC not determined. Reproduced with permission from Pfaller MA et al.[1]

STUDY CONCLUSIONS

- The distribution of *Candida* species in the relatively small phase 2 study was similar to what has been reported in the literature for BSIs[1,4,9]
- Anidulafungin was efficacious in eradicating many *Candida* spp from the bloodstream and other normally sterile sites[1]
- Eradication rates in the evaluable population showed a dose-related trend (Figure 1)[1]
- Eradication rates for the more commonly isolated species were comparable to the eradication rate for all species combined[1]
- Clinical success was not related to the anidulafungin MIC for the isolates studied[1]
  - *C parapsilosis* accounted for most MICs >1 µg/mL, but the eradication rate was high (6 of 7 isolates) even for this species[1]

HIGHLIGHTS[1]

- This study demonstrated that anidulafungin is efficacious in eradicating *Candida* spp in invasive candidiasis
- Eradication rates showed a trend toward a dose–response relationship with anidulafungin

References: 1. Pfaller MA, Diekema DJ, Boyken L, et al. Effectiveness of anidulafungin in eradicating *Candida* species in invasive candidiasis. *Antimicrob Agents Chemother.* 2005;49:4795-4797 (Pfaller 2005). **2.** Wilson LS, Reyes CM, Stolpman M, Speckman J, Allen K, Beney J. The direct cost and incidence of systemic fungal infections. *Value Health.* 2002;5:26-34. **3.** Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis.* 2004;39:309-317. **4.** Diekema DJ, Messer SA, Brueggemann AB, et al. Epidemiology of candidemia: 3-year results from the Emerging Infections and the Epidemiology of Iowa Organisms study. *J Clin Microbiol.* 2002;40:1298-1302. Cited by: Pfaller 2005. **5.** Pfaller MA, Diekema DJ, for the International Fungal Surveillance Group. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*. *Clin Microbiol Infect.* 2004;10(suppl 1):11-23. **6.** Moore CB, Oakley KL, Denning DW. In vitro activity of a new echinocandin, LY303366, and comparison with fluconazole, flucytosine and amphotericin B against *Candida* species. *Clin Microbiol Infect.* 2001;7:11-16. Cited by: Pfaller 2005. **7.** Arévalo MP, Carrillo-Muñoz A-J, Salgado J, et al. Antifungal activity of the echinocandin anidulafungin (VER002, LY-303366) against yeast pathogens: a comparative study with M27-A microdilution method. *J Antimicrob Chemother.* 2003;51:163-166. Cited by: Pfaller 2005. **8.** Krause DS, Reinhardt J, Vazquez JA, et al. Phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in invasive candidiasis and candidemia. *Antimicrob Agents Chemother.* 2004;48: 2021-2024. Cited by: Pfaller 2005. **9.** Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis.* 2003;37:1172-1177. Cited by: Pfaller 2005.

Please see Important Safety Information poster displayed in this room.
Please see full Prescribing Information available in this room.

Pfizer U.S. Pharmaceuticals

Eraxis™ (anidulafungin IV)