Echinocandins target the 1,3-β-D-glucan synthase enzyme complex. Mutations in the PKS genes, which encode the catalytic subunit of this complex, have been associated with reduced susceptibility to echinocandins and increased clinical failures. These “hot spot” (HS) regions within PKS genes (“HS1 and HS2”, encoding 9 and 8 amino acids, respectively) are most often associated with reduced susceptibility to echinocandins.

CD101 is a novel, long half-life echinocandin undergoing clinical development for the treatment of candidemia and invasive candidiasis. A front-loaded treatment paradigm may have advantageous effects on the efficacy and practicality of this drug, compared to currently available agents. The potential for clinically relevant Candida spp. to develop resistance to front-loaded regimens was evaluated to determine whether the emergence of resistance was possible.

In this study, the potential for genotypic and phenotypic emergence of resistance to CD101 in Candida spp. was evaluated for the treatment of candidemia and invasive candidiasis.

Patients with candidemia were recruited from 3 clinical centers and the Candida isolates were selected for their high MIC of CD101. Serial passage testing demonstrated the emergence of resistance to CD101 in Candida parapsilosis and Candida glabrata.

**Methods:**
- Serial passage studies were conducted using CD101 and comparator echinocandins (ANID and CAS) and comparator antifungals (5-FK, P20, and P20) for 20 passages.
- Strains: Representative wild-type strains of C. albicans (NRRL Y-4747), C. parapsilosis (ATCC 90030), and C. glabrata (ATCC 6258) were used in this study.
- MIC determination: MIC plates were read following a 24-hour incubation at 35°C and 37°C.
- Sequencing: Hot spot mutations (HS mutations) were sequenced in C. parapsilosis and C. glabrata following 4 and 8 passages, respectively.

**Results:**
- Resistance to CD101 emerged in both C. parapsilosis and C. glabrata following 20 passages.
- Reduced susceptibility to CD101 was observed for all 3 echinocandins.
- C. glabrata strains had the most consistent high MIC shifts at P20 for all drugs, followed by C. albicans and finally C. parapsilosis.
- The lowest potential of resistance to all strains tested was observed for P20.

**Conclusions:**
- The potential for resistance development to CD101 among 4 key clinically-relevant Candida species was low.
- CD101 had the smallest overall MIC fold-shift increases at passage 20.
- Consistent with clinical observations and its haploid nature, C. glabrata demonstrated the highest potential for echinocandin resistance.
- Cross-resistance was broadly observed among the three echinocandins evaluated.
- With the exception of C. Anidulafungin was used for both strains with the lowest MIC shifts possessed the lowest fold-shift potential. NO.
- In addition, all MIC fold-shift tendencies were similar to CAS and in vitro activity, with the exception of C. parapsilosis and C. albicans.

**References:**

**Acknowledgements:**
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