The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the echinocandins favor infrequent administration of large doses. The in vivo investigation reported here tested the utility of a range of humanized dose levels of micafungin using a variety of prolonged dosing intervals for the prevention and therapy of established disseminated candidiasis. Humanized doses of 600 mg administered every 6 days prevented fungal growth in prophylaxis. Humanized doses of 300 to 1,000 mg administered every 6 days demonstrated efficacy for established infections.

Several pharmacokinetic and pharmacodynamic (PK/PD) characteristics help to discern optimal antimicrobial dosing frequency. Drugs that exhibit concentration-dependent killing and prolonged postantibiotic effects are most effective when larger dose levels are administered infrequently (1–3). Intuitively, drugs with prolonged elimination half-lives can also be given less frequently than drugs that are rapidly cleared. In addition to enhancing efficacy, extended-interval dosing has the potential to reduce the length of hospitalization, to improve patient compliance and satisfaction, and to reduce the cost of drugs that require parenteral administration.

The characteristics of several antibacterial and antiviral compounds have led to less than daily or even weekly dosing intervals (4, 5). These concepts have more recently been considered for antifungal drugs meeting these PK/PD criteria in the settings of fungal infection prevention (prophylaxis) and therapy (6–9).

FIG 1 Prophylaxis study design and in vivo efficacy of micafungin for prevention of invasive candidiasis. (A) Study schematic showing the timing of therapy, infection time points, and study duration. (B) Micafungin prophylaxis data with C. albicans K1. (C) Micafungin prophylaxis data with C. albicans 98–17. The x axis represents the dose level that was humanized in mice. The y axis represents the burden of organisms in mouse kidneys. Each vertical bar represents the mean and standard deviation of data from four mice. Untreated control data are represented by the black vertical bar. Each colored bar represents a different day of infection after micafungin therapy. The solid horizontal line represents the burden of organisms in mice 1 h after infection (net stasis endpoint).
Drugs from the polyene and echinocandin antifungal drug classes possess the PK/PD qualities that would support the concept of extended-interval dosing (10–18). Furthermore, the relatively wide therapeutic window for the echinocandins suggests the ability to safely escalate dose levels for several of these compounds nearly 10-fold higher than the dose levels approved for daily therapy (19–25).

A number of preclinical and clinical pharmacokinetic and treatment studies have explored dosing intervals beyond traditional daily dosing. For example, preclinical in vivo dose fractionation studies with the echinocandins demonstrated efficacy with once-weekly dosing (10,12, 26). Additionally, dosing every other day with micafungin (300 mg every other day) for esophageal candidiasis was shown to be just as effective as or more effective than the standard dosing levels with daily therapy (100 mg/day) (6).

The current in vivo studies were designed to test the efficacy of extended-interval dosing with micafungin in the setting of prophylaxis and therapy for Candida. Dosing regimens in mice were humanized to mimic micafungin pharmacokinetics with five dose levels ranging from 100 to 1,000 mg (19, 21, 27, 28). The specific goal of the investigations was to identify the longest dosing interval for which humanized doses would provide either infection prevention or treatment efficacy for an established infection. We hypothesized that these novel dosing strategies would be similarly efficacious as or more efficacious than standard regimens (29).

The persistently neutropenic, murine disseminated-candidiasis model (tail vein) was used for all treatment studies. Two micafungin-susceptible strains of C. albicans (strain K1 with an MIC of 0.03 μg/ml and strain 98-17 with an MIC of 0.06 μg/ml) were chosen based upon prior experience in the infection model (10, 30, 31). For the prophylaxis study design, groups of four mice were treated with five dose levels of micafungin to mimic the pharmacokinetics of human doses of 100, 200, 300, 400, and 600 mg in healthy volunteers. The regimens in mice correlating to these regimens were 4, 8, 12, 16, and 24 mg/kg of body weight given by the intraperitoneal route and were chosen to match the area under the concentration-time curve from 0 to 24 h (AUC0–24) of the serum. Pharmacokinetic linearity in mice and humans as well as the similarity in elimination half-lives aided considerably in humanizing the murine regimens. Following single-dose prophylaxis with micafungin, groups of mice were challenged with an intravenous inoculum (10^3.5 ± 0.5 CFU/ml) of Candida at one of 6 increasing time points (0, 0.5, 1, 2, 4, and 6 days after micafungin treatment). This design was intended to mimic an organism burden lower than that of established infection and to discern the dose and time after dosing that are protective against infection during antifungal prophylaxis. Twenty-four hours after infection, the burden of Candida in mouse kidneys was assessed in each treatment and control group (Fig. 1). In untreated control mice, the organism burden of Candida increased 10^2.2 ± 0.5 CFU/kidneys. The 100-mg daily dose in clinical use prevented organism growth compared to the burden at the start of therapy (stasis) for up to 4 days after therapy. The humanized doses of 400 and 600 mg of micafungin prevented organism recovery for up to 6 days. These data suggest prolonged effective micafungin tissue residence times as previously shown for caspofungin (13). The results support the current clinical exploration of weekly prophylaxis with the echinocandins using dose levels of 400 to 600 mg/week. This treatment option may be particularly attractive for patients with unavoidable triazole-chemotherapy drug interactions or for high-risk solid-organ transplant recipients.

FIG 2 Established infection study design and in vivo efficacy of micafungin for treatment of invasive candidiasis. (A) Study schematic showing the timing of infection and the timing and dosing intervals for micafungin therapy and study duration. (B) Micafungin treatment data with C. albicans K1. (C) Micafungin treatment data with C. albicans 98-17. The x axis represents the dose level that was humanized in mice. The y axis represents the burden of organisms in mouse kidneys. Each vertical bar represents the mean and standard deviation of data from four mice. Untreated control data are represented by the black vertical bar. Each colored bar represents a different dosing interval for micafungin therapy (QD, once a day; Q3D, every 3 days; etc.). The solid horizontal line represents the burden of organisms in mice 1 h after infection (net stasis endpoint).
The same neutropenic infection model was utilized to test the impact of dosing interval extension for humanized micafungin dosing regimens on treatment outcome in established disseminated candidiasis (Fig. 2). An infecting inoculum of Candida of 10^6–4 ± 0.05 CFU/ml was similar to that used in PK/PD studies of established disseminated candidiasis with other antifungals in this model (10, 32, 33). In untreated control animals, the burden of organisms in the kidneys increased 10^3.6 ± 0.72 CFU/kidneys over the study period. Following infection, mice were treated with five micafungin dose levels that mimicked human pharmacokinetics with doses of 100, 300, 600, 800, and 1,000 mg. The 100-mg dose was administered daily, which is consistent with standard micafungin therapy for invasive candidiasis (34). The higher dose levels were administered every 3, 6, or 12 days over the 12-day study. Organism burden was assessed as described above at the beginning and end of therapy. The humanized 100 mg/day regimen and each regimen of 300 mg or higher administered every 6 days for disseminated candidiasis in mice with persistent neutropenia. Antimicrob Agents Chemother 70:1527–1530. http://dx.doi.org/10.1128/AAC.01939-14.


