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Clinical Pharmacodynamic Index Identification for Micafungin in Esophageal Candidiasis: Dosing Strategy Optimization

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Echinocandins exhibit concentration-dependent effects on *Candida* species, and preclinical studies support the administration of large, infrequent doses. The current report examines the pharmacokinetics/pharmacodynamics of two multicenter, randomized trials of micafungin dosing regimens that differed in both dose level and dosing interval. Analysis demonstrates the clinical relevance of the dose level and area under the concentration-time curve (AUC). Better, although not statistically significant ($P = 0.056$), outcomes were seen with higher maximum concentrations of drug in serum (C_{max}) and large, infrequent doses. The results support further clinical investigation of novel micafungin dosing regimens with large doses but less than daily administration. (These studies have been registered at ClinicalTrials.gov under registration no. NCT00666185 and NCT00665639.)

Understanding the pharmacodynamics driver of antimicrobial efficacy provides a means to identify the optimal dosing strategy (1, 2). Ideal dosing of antimicrobials for which the maximum concentration of drug in serum (C_{max}) and MIC are most closely linked to the desired effect would involve the infrequent administration of large doses. Conversely, when the area under the concentration-time curve over 24 h in the steady state divided by the MIC (AUC/MIC ratio) is best predictive of outcome, it is the total amount of compound rather than the dosing frequency that impacts the treatment strategy. The clinical utility of this information has long been recognized with the C_{max}-linked aminoglycoside drug class, for which once-daily administration both improves efficacy and reduces toxicity (3, 4). More recently, clinical studies have identified enhanced efficacy for extended and continuous infusion of beta-lactams in the critical care setting, an approach to dosing which optimizes the percentage of time above the MIC, the pharmacokinetic/pharmacodynamic (PK/PD) index associated with efficacy (5–7).

The majority of the data available to determine the ideal pharmacodynamic dosing strategy is the product of preclinical *in vitro* and *in vivo* dose fractionation studies. While clinical studies may use different dose levels, the evaluation of more than a single dosing interval is uncommon. The goal of the present analysis was to utilize an existing clinical data set for an antifungal agent, micafungin, in which both the dose and the dosing interval were varied in order to identify the optimal dosing strategy.

Experimental infection models have consistently found concentration-dependent killing and prolonged postantifungal effects for the echinocandin class (8–18). Dose fractionation and pharmacokinetic/pharmacodynamic (PK/PD) index analysis have demonstrated the importance of both the C_{max}/MIC and AUC/MIC indices to predict efficacy.

In the present investigation, micafungin PK and efficacy were explored using pooled data from two multicenter, double-blind, randomized clinical trials in which adult patients were treated for esophageal candidiasis. The two studies were completed in 2002 (sponsor study 03-7-005/NCT00666185) and 2004 (Astellas study 03-7-008/NCT00665639) (19). The study protocols were identical with regard to disease diagnosis, treatment duration, and study endpoint determination. Both clinical trials, which were approved by the Institutional Review Board or Ethical Review Committee and received relevant regulatory approvals in each country, were conducted in accordance with good clinical practice guidelines; written informed consent was obtained from all study participants prior to the start of each trial. The two treatment regimens compared were 150 mg micafungin every day (QD) and 300 mg micafungin every other day (QOD) administered for a minimum of 14

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TABLE 1 Efficacy of micafungin[a]

Micafungin dosing regimen	No. (%) of patients with indicated result					
	Mycological response at end of therapy*			Clinical relapse at 2 weeks posttreatment**		
	Success	Failure	Total	Yes	No	Total
150 mg QD	145 (78.8)	39 (21.2)	184	22 (12.2)	159 (87.9)	181
300 mg QOD	115 (87.1)	17 (12.9)	132	7 (5.6)	119 (94.4)	126
Total	260	56	316	29	278	307

[a] *, $P = 0.056$; **, $P = 0.051$; QD, daily; QOD, every other day.

TABLE 2 Summary statistics of predicted steady-state AUC_{0-48} and C_{max} by micafungin dosing regimen

Dosing regimen	AUC_{0-48} (μg · h/ml)		C_{max} (μg/ml)		C_{min} (μg/ml)	
	Mean (CV%)	Median (minimum, maximum)	Mean (CV%)	Median (minimum, maximum)	Mean (CV%)	Median (minimum, maximum)
150 mg QD ($n = 188$)[a]	310 (12.9)	304 (205, 582)	14.4 (9.43)	14.2 (10.4, 21.4)	3.49 (17.8)	3.41 (1.90, 8.38)
300 mg QOD ($n = 132$)	311 (15.6)	303 (244, 616)	23.7 (7.28)	23.5 (18.3, 33.6)	1.77 (33.8)	1.66 (0.949, 5.72)

[a] Since one patient from this group had no PK data and was missing weight data, individual and mean population predicted exposures, respectively, could not be estimated.

days and up to 21 days. It was hypothesized that use of the higher-dosage but less frequently administered regimen would be associated with efficacy either superior or equivalent to that seen with the standard dose daily regimen based upon achieving a higher C_{max} or similar AUC, respectively. Both endoscopically obtained microbiologic and histopathologic success at the end of therapy and clinical relapse 2 weeks after the end of therapy were considered in the current analysis. The per-protocol data sets, which included patients with biopsy-proven disease and who received at least 10 doses of micafungin, were evaluated. The study arms included 189 patients in the 150 mg QD group and 132 study participants receiving the QOD regimen. Patient demographics were statistically similar in the two studies and the two treatment arms (see Table S1 in the supplemental material). The majority of patients carried an HIV diagnosis. Pooled data from the two studies were used to assess the PK/PD relationships for the two treatment groups. The two binary study outcomes were compared for the two treatment groups using the χ^2 test or the Fisher exact test, and statistical significance was defined by a P value ≤ 0.05. Plasma samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h after infusion on days 1 and 11. Samples were analyzed for the level of micafungin by using solid-phase extraction and reverse-phase high-performance liquid chromatography as previously described (20–24). A previous population PK model was developed for micafungin across multiple studies ($n = 4$), utilizing drug concentration data from 364 patients, including a subset of 67 patients from the two clinical studies described here (25). In the above-described population PK model, body weight was a statistically significant predictor of micafungin clearance. Individual *post hoc*-predicted PK parameters from the 53 patients who received the two dosing regimens of interest for this analysis and were in the pertinent protocol set were used to simulate plasma micafungin concentrations over a 48-h period at the steady state for the purposes of calculating C_{max} and AUC from 0 to 48 h (AUC_{0-48}). Population mean PK parameters were instead used to estimate C_{max} and AUC_{0-48} values for the 267 patients in the per protocol who did not have measured plasma PK data available for analysis.

An endoscopically proven mycological response at the end of therapy was observed in 78.8% of patients in the 150 mg QD group and 87.1% in the 300 mg QOD group (Table 1 [$P = 0.056$]). While these outcomes were not statistically significant, there was a numerically higher efficacy rate in the higher-dose, extended-interval arm. The treatment outcomes for the two regimens were also similar for the relapse endpoint, with failure rates of 12.2% in the daily administration group and 5.6% in the high-dose arm (Table 1 [$P = 0.051$]). A comparison of exposure measurements for the two dosing regimens at the steady state is presented in Table 2. As previously shown in other dose escalation studies (26, 27), pharmacokinetics increased in a linear manner with dose. Steady-state AUC_{0-48} values for the two dosing regimens were comparable. The median C_{max} was 1.65-fold higher whereas the median C_{min} was 0.49-fold lower for the 300 mg than for the 150 mg group (Wilcoxon rank sum test $P < 0.0001$ [comparisons of C_{max} and C_{min}]).

The present dose escalation and dosing-interval clinical study pharmacodynamic analysis is congruent with preclinical studies which demonstrate the importance of the AUC/MIC and C_{max}/MIC concentration-dependent indices. While these outcomes were not statistically significant, there was a numerically higher efficacy rate in the higher-dose, extended-interval arm. These observations support the idea of treatment strategies that optimize both C_{max} and AUC.

Prior safety studies have not identified a clear maximal tolerated dose for micafungin; however, doses as high as 600 mg have been generally well tolerated (28, 29). It is possible that dose levels even higher than the 300 mg used in this study and less-frequent administration could offer additional clinical benefits compared to the currently approved daily regimens. While this strategy cannot be recommended for clinical use outside treatment of mucosal candidiasis, there may be other situations in which it could be appropriate given more supportive data. In addition, as the inevitable process of resistance emergence becomes a relevant issue for the echinocandin class, these novel dosing strategies may provide useful treatment options. Unfortunately, accurate susceptibility testing was not available to allow us to explore the impact of MIC on outcome in the study. However, as the majority of isolates were *Candida albicans* isolates, we do not believe the collection would have included very many strains with higher drug MICs or species such as *C. parapsilosis* or *C. guilliermondii*. At a minimum, the results of this evaluation provide an intriguing rationale for future clinical investigation of higher echinocandin doses and extended dosing intervals.

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