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# Optimization of Dosage Regimen of Rezafungin against *Candida spp*. Based on Pharmacokinetic/Pharmacodynamic Analysis

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## Abstract

Invasive candidiasis was the most common nosocomial fungal infection with high morbidity and mortality, which is mainly occurring in immunodeficiency and critical patients. Echinocandins were recommended as first-line drugs for the treatment and prevention of invasive candidiasis. In our study, we aimed to optimize the dosage of Rezafungin against *Candida spp.* based on pharmacokinetic/pharmacodynamics (PK/PD) analysis. We collected the published data about pharmacokinetic parameters of rezafungin and the MIC distribution of *Candida spp.* on rezafungin. Monte Carlo simulation was used to calculate probability of target attainment and a cumulative fraction of response to assess the best dosing regimen. The optimal dosage regimen for *C. albicans* and *C. glabrata* was 50 mg IV, and the optimal dosage regimen for *C. parapsilosis* was 100 mg IV. Lastly, rezafungin has an excellent antifungal effect on *C. albicans*, *C. glabrata* and *C. parapsilosis*.

## Keywords

Invasive Candidiasis, Rezafungin, Pharmacokinetics/Pharmacodynamics, Monte Carlo Simulation

## 1. Introduction

Invasive candidiasis has the most common nosocomial fungal infections, mainly in immunodeficiency and critically ill patients, with high morbidity and mortality. Some studies reported that patients were diagnosed with invasive candidiasis, which mortality rate is 35% at 12 weeks, even as high as 50% [1] [2]. Since 2009, Echinocandins have been recommended as first-line drugs for the treat-

ment and prevention of invasive candidiasis, as well as suspected candidiasis in patients with neutropenia and non-neutropenia experience medication [3] [4].

Rezafungin is a new generation of echinocandins antifungal drugs that can be against *Candida spp.* cells by inhibiting the synthesis of $\beta$-1,3-D-glucan synthase [5]. Rezafungin is a long half-life of up to 133 hours [6] and is given only by intravenous administration once a week. The antifungal activity of rezafungin for *Candida spp.* and *Aspergillus spp.* was similar to that of existing echinococcus *in vitro*. It has antifungal effects on drug-resistant strains such as azole-resistant *Aspergillus spp.* and *Candida auris* and *Candida glabrata* [7] [8] [9]. Rezafungin is currently undergoing a phase III clinical trial [10]. At present, only 3 species of *Candida spp*. were published in PK/PD targets of Rezafungin against *Candida spp*. (*C. albicans*, *C. glabrata*, *C. parapsilosis*). So in this study, based on pharmacokinetic/pharmacodynamic (PK/PD) parameters, we used Monte Carlo simulation (MCS) to optimize rezafungin dosage in treatment for 3 *Candida spp*., in order to provide a basis for clinical research.

## 2. Material and Methods

### 2.1. Pharmacokinetic/Pharmacodynamic (PK/PD) Parameters

The PK parameters of Rezafungin were derived from published literature [6], and the data are derived from the results of single-dose measurements in healthy adult persons. The specific data were shown in **Table 1**. Rezafungin is a concentration-dependent antifungal drug [11]. The plasma protein binding rate was 98% [12].

### 2.2. Minimum Inhibition Concentration (MIC) Distribution of *Candida spp*.

MIC distribution of Rezafungin for *Candida spp*. comes from the US SENTRY Program between 2016 and 2018 [13], shown in **Table 2**.

**Table 1.** Pharmacokinetic parameters of rezafungin in healthy adults.

| Subjects | dose (mean ± sd) | | | |
|---|---|---|---|---|
| | 50 mg | 100 mg | 200 mg | 400 mg |
| $C_{max}$ (μg/ml) | 2.76 ± 0.574 | 4.86 ± 0.561 | 10.9 ± 2.17 | 22.7 ± 3.59 |
| $t_{1/2}$ ( h) | 133 ± 6.62 | 146 ± 3.82 | 125 ± 13.0 | 129 ± 18.6 |
| AUC (μg·hr/mL) | 145 ± 20.4 | 254 ± 22.9 | 592 ± 66.8 | 1160 ± 170 |
| CL (L/h) | 0.225 ± 0.0378 | 0.240 ± 0.0196 | 0.219 ± 0.0230 | 0.226 ± 0.0421 |

**Table 2.** MIC distribution of Rezafungin for *Candida spp.*

| Species | n | MIC ( μg/ml) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.002 | 0.004 | 0.008 | 0.016 | 0.032 | 0.064 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 |
| *C. albicans* | 835 | 11 | 6 | 87 | 270 | 309 | 139 | 28 | 2 | | | | |
| *C. glabrata* | 374 | 1 | 0 | 0 | 5 | 136 | 162 | 54 | 6 | 3 | 3 | 4 | |
| *C. parapsilosis* | 329 | | | 0 | 1 | 0 | 0 | 1 | 5 | 62 | 134 | 124 | 2 |

### 2.3. Monte Carlo Simulation (MCS)

MCS evaluates antifungal dosage regimens by integrating pharmacokinetic (PK) parameters, Minimum Inhibitory Concentration (MIC) distribution, and pharmacodynamics (PD) parameters. Crystal Ball (version 11.1.2.4.600, Oracle) software was used for Monte Carlo Simulation to obtain a probability of target attainment (PTA) and a cumulative fraction of response (CFR) for each dosing regimen of rezafungin in healthy adults. The PK/PD parameters of rezafungin were expressed in AUC/MIC ratio. The target value of *C. albicans* was 2.92, the target value of *C. glabrata* was 0.07, and the target value of *C. parapsilosis* was 2.61 [11]. The formula [14] is

$$\mathrm{fAUC/MIC} = \left(\mathrm{f} \times \mathrm{dose}\right) / \left(\mathrm{CL} \times \mathrm{MIC}\right)$$

where CL follows a lognormal distribution, dose (mg) and f follow a uniform distribution, and MIC follows a custom distribution. CFR ≥ 90% is considered as the best plan, and the formula is as follows:

$$\mathrm{CFR} = \sum_{i=1}^{n} \mathrm{PTA}_i \times \mathrm{F}_i$$

## 3. Results

### 3.1. PTA Analysis

PTA Analysis of Rezafungin in healthy adults for 3 *Candida spp*. (*C. albicans*, *C. glabrata*, *C. parapsilosis*) were shown in **Figure 1**. The results showed that PTA values were more than 90% for *C. albicans* when MIC was less than 0.25 μg/ml in each dosing regimen. For *C. glabrata*, each dosing regimen of rezafungin attained the PTA when MIC was less than 2 μg/ml. As *C. parapsilosis* for PTA with more than 90%, MIC of rezafungin 50 mg, 100 mg, 200 mg and 400 mg were less than 1 μg/ml, 2 μg/ml, 4 μg/ml and 4 μg/ml, respectively.

### 3.2. CFR Analysis

The CFR of different dosing regimens of rezafungin in a single dose of healthy adults were shown in **Table 3**. The results showed that rezafungin had an excellent antifungal effect in the treatment of *C. albicans* and *C. glabrata*, with a CFR more than 90%. The CFR with 69.35% for *C. parapsilosis* indicated that the antibacterial effect of rezafungin 50 mg IV administration regimen was weak. The other treatment regimens of rezafungin had sound antibacterial effects.

**Table 3.** CFR values (%) of *C. albicans*, *C. glabrata*, *C. parapsilosis* under different dosing regimens of rezafungin.

| Species | CFR (%) | | | |
|---|---|---|---|---|
| | 50 mg | 100 mg | 200 mg | 400 mg |
| *C. albicans* | 100 | 100 | 100 | 100 |
| *C. glabrata* | 100 | 100 | 100 | 100 |
| *C. parapsilosis* | 69.35 | 99.41 | 100 | 100 |

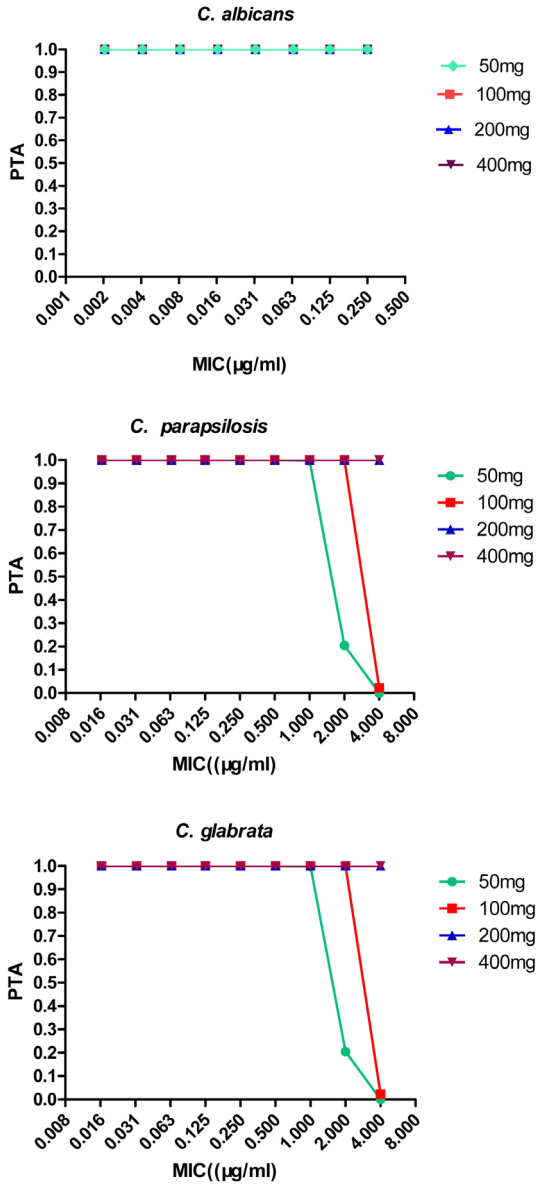


**Figure 1.** PTA of rezafungin estimated at different administration dosage in patients with *Candida spp*. Different letters represent different *Candida spp.* (*C. albicans*, *C. glabrata*, *C. parapsilosis*).

## 4. Discussion

Rezafungin in this study was a new antifungal medicine of echinocandins, which had an excellent antifungal effect. The *in vitro* test results show that it has an extraordinary antifungal impact on some resistant strains. In this study, based on PK/PD analysis, Monte Carlo simulation was used for the first time to obtain the PTA and CFR of rzafungin against three *Candida spp*. (*C. albicans*, *C. glabrata*, *C. parapsilosis*), and *C. albicans and C. glabrata* can get good antifungal effect at 50 mg IV, while *C. parapsilosis* can get the good antibacterial effect at 100 mg IV.

A large number of studies had shown that the current anti-fungal drug dosing

regimens have a weak impact on *C. glabrata*. For example, platinum isavuconazole had a max CFR value of 80.68% under different dosing regimens [15]. Isavuconazole had a max CFR value of 62.70% under different dosing regimens [16]. In this study, Monte Carlo simulation analysis showed that rezafungin in healthy people could obtain good results when the dosage is 50 mg, which provides a basis for subsequent clinical research and application.

Monte Carlo simulation used a combination of drug PK/PD parameters and microbial MIC distribution to simulate the dosage selection of each fungus to determine and optimise the dosing regimen, but it had some limitations. Rezafungin had completed phase II clinical trials and was in phase III clinical trials, the data about AUC/MIC for different species of *Candida spp.* are less, only 3 *Candida spp*. were sdudied, they are *C. albicans*, *C. glabrata*, *C. parapsilosis*. The sample size of *Candida spp.* MIC distribution research was limited. The samples were all only the pharmacokinetics of serum was considered, but body fluids in other sites were not considered.

## 5. Conclusion

In conclusion, the results of PK/PD modelling and Monte Carlo simulations suggest that rezafungin had a good antibacterial effect on *C. albicans*, *C. glabrata*, *C. parapsilosis*. The best dosing for *C. albicans* and *C. glabrata* is 50 mg IV and the best dosing regimen for *C. parapsilosis* is 100 mg IV.

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## Conflicts of Interest

The authors declare no conflict of interest.

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