2324

Influence of Dose Size on Dose Response Relationships for Linezolid Efficacy Using Monte Carlo Simulations

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ABSTRACT

Purpose. Phase II linezolid (LZD) data analyses suggested that AUC_{0-24}/MIC ratio was an important predictor of efficacy outcome. Monte Carlo simulations were performed to determine whether dose size influences both the proportion of patients with MRSA at risk for suboptimal AUC/MIC ratios when administered LZD 500 or 600 mg BID regimens and the expected cure rates.

Methods. Steady-state concentration-time profiles for typical 50 year old white males weighing 82 kg receiving LZD 500 or 600 mg BID were simulated in NONMEM. The MIC's for MRSA were simulated based on the distribution in U.S. LZD studies. Frequency distributions from random AUC/MIC pairing were used to derive probability densities for each dose. Expected cure rates were examined using a PD model developed from previous logistic regression analysis of LZD.

Results. Simulated patients had a greater probability of an AUC/MIC ratio in the lower portion of the curve when the LZD dosage was 500 mg as compared to 600mg BID. The expected cure rate was 70.0% (95%CI 69.8, 70.2) given a 500 BID dosage and 74.1% (95% CI 69.8, 70.2) with 600 mg BID (p< 0.05).

Conclusions. These results support selection of a 600 mg BID regimen of LZD based on the increased probability of suboptimal AUC/MIC ratios when administered LZD 500 mg BID. Based on these simulations, for every 100 patients treated with a LZD 600 BID regimen, more than an additional 4 patients are expected to be successfully treated as compared to the 500 mg BID regimen.

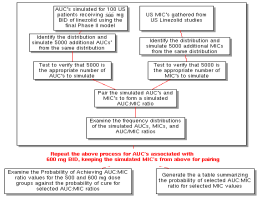
INTRODUCTION

The development of a therapeutic response relationship requires knowledge of drug exposure (e.g., area under the concentration time curve (AUC)) and a measure of drug potency (e.g., minimum inhibitory concentration (MIC)). Pharmacodynamic analyses of the Phase II linezolid data collected in US studies suggested that AUC:MIC ratio was an important predictor of outcome.

Inter-subject variability in pharmacokinetics and MIC variability in infected patients may impact the probability of attaining optimal AUC:MIC ratios and favorable outcomes. Monte Carlo simulation was performed in this analysis to obtain estimates of the expected distribution of the AUC:MIC ratio estimates for typical patients with methicillin-resistant Staph aureus (MRSA) receiving 500 versus 600 mg twice daily dosing regimens of linezolid. This approach allowed comparison of the probability of achieving sub-optimal AUC:MIC ratios and probability of patient cure at each dose level using a pharmacodynamic model previously developed from logistic regression analyses of linezolid response. The logistic regression analysis was performed using data from 73 patients enrolled in the Phase II bacteremia (BAC) trial for linezolid of which 76.7% were cured of their infection.

METHODS

Monte Carlo Simulation Study Procedures



METHODS (continued)

Pharmacodynamic Analyses

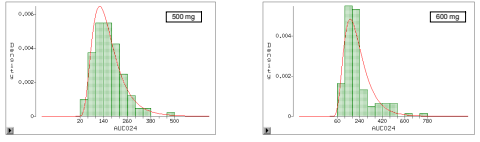
- **AUC:MIC Ratio:**
  - Calculated using the trapezoidal rule method on the predicted concentration-time profile.
  - The ratio was formed by dividing AUC_{0-24} by the MIC value.
- **Cure Rate Calculation:** The probability of cure was calculated for the mean AUC:MIC ratio for each dose group. This probability was multiplied by 100% to obtain mean % cure rate.
- **Outcome Evaluation:** Clinical and microbiologic efficacy at the long-term follow-up.
- **Logistic Regression:**
  - Logistic analyses with stepwise selection.
  - Endpoints evaluated: clinical, microbiologic, and combination (clinically cured or improved and microbiologic success).
  - Predictors of failure evaluated: AUC:MIC ratio, length of time above the MIC, age, gender, weight, total daily dose.
  - An alpha = 0.05 (1 degree of freedom) was used to define statistical significance for the addition of a single parameter and an alpha = 0.01 (1 degree of freedom) was used for the deletion of a single parameter.

RESULTS

Pharmacokinetic Simulations:

•As shown in **Figure 1** the distribution of the simulated AUC's for the initial 100 subjects (50 year old, 82 kg, male) approximates a log normal distribution.

FIGURE 1. Density of NONMEM simulated AUC log normal curve overlaid 500mg and 600mg (n=100) for 82 kg simulated patient.



- **Table 1** shows that the majority of the MRSA organisms had a measured linezolid MIC value of 2.

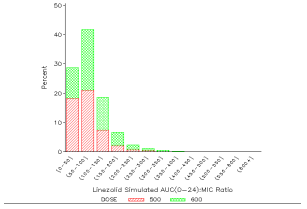
TABLE 1. Number (%) of MICs to be Paired with Monte Carlo Simulated AUCs

MIC	N(%)
0.25	4 (0.08)
1.0	263 (5.27)
2.0	3033 (60.66)
4.0	1692 (33.83)
8.0	8 (0.16)
Total	5000 (100.0)

RESULTS (continued)

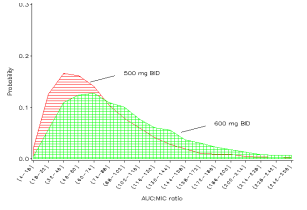
•**Figure 2** shows the histogram of Monte Carlo simulated AUC:MIC ratios for the two patient populations receiving 500 mg versus 600 mg of linezolid BID.

FIGURE 2. Histogram of Monte Carlo simulated AUC:MIC Ratio 500 mg (n=5,000) and 600 mg BID (n=5 ,000) for 82 kg simulated patient.



•**Figure 3** shows the probability density of Monte Carlo simulated AUC:MIC ratios for 500 mg and 600 mg of linezolid BID for 82 kg simulated patient.

FIGURE 3. Probability density of Monte Carlo simulated AUC:MIC ratio for 500 mg and 600 mg BID for 82 kg simulated patient.



•Simulated patients weighing 82 kg had a greater probability of achieving higher AUC:MIC ratios when given 600 mg versus 500 mg of linezolid administered twice daily as shown in **Table 2**.

TABLE 2. Probability of Achieving an AUC:MIC Ratio ≥ a Specified Value, Stratified by MIC, for 82 kg Simulated Patients

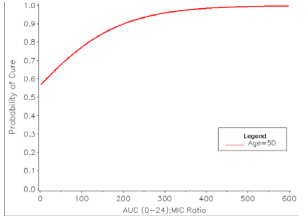
BID		AUC:MIC Ratio					
Dose (mg)		> 50	> 75	> 100	> 125	>150	>175
MIC	**500**	61.4%	34.4%	17.9%	8.4%	3.8%	2.0%
> 2	**600**	78.0%	54.6%	35.0%	21.7%	12.5%	7.2%
MIC	**500**	26.6%	7.2%	1.9%	0.5%	0.2%	0.2%
> 4	**600**	49.8%	19.6%	7.4%	3.1%	0.8%	0.8%

RESULTS (continued)

Pharmacodynamic Simulations:

- Logistic regression analysis of the 73 patients in the Phase II BAC study of linezolid demonstrated a statistically significant association between the AUC:MIC ratio and probability of cure.
- The analysis of time above the MIC was not informative; the majority of patients were above the MIC for the majority of their dosing interval.
- The probability of clinical cure is greater at higher AUC:MIC ratios for simulated patients with bacteremia as shown in **Figure 4** .

FIGURE 4. Probability of clinical cure for BAC.



- The median AUC:MIC ratio observed in the BAC study was 122.9. Of the patients who achieved an AUC:MIC ratio < or = this median value, 66.7% achieved clinical cure.
- **Table 3** demonstrates that the expected cure rate is higher when 600 mg twice daily is administered versus 500 mg of linezolid twice daily. The expected cure rate for the 600 mg twice daily regimen is 74.1% which agrees with the 76.6% cure rate observed in the Phase II bacteremia study.

TABLE 3. Expected Cure Rates for Patients Receiving Linezolid 500 and 600 mg BID

Weight (kg)	BID Dose (mg)	Expected Cure Rate (%)	95% Confidence Intervals about the Cure Rate
82.2	500	70.0	(69.8, 70.2)
	600	74.1	(73.8, 74.3)

CONCLUSION

- **These simulation results support selection of a 600 mg BID regimen of LZD based on the increased probability of a successful AUC:MIC ratio when administering LZD 600 mg BID compared to 500 mg BID.**
- **Based on these simulations, for every 100 patients treated with a LZD 600 mg BID regimen, more than an additional 4 patients are expected to be successfully treated as compared to the 500 mg BID regimen.**
- **From the derived pharmacodynamic relationship, the expected cure rate for the 600 mg twice daily regimen is 74.1% which is consistent with the 76.6% cure rate observed in the linezolid Phase II bacteremia study.**
- **Based on these simulations, the ability to evaluate alternative regimens for antibiotics is demonstrated.**