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Population Pharmacokinetic (PK) Analysis of the Fixed Dose of Iclaprim in the Phase 3 REVIVE Studies for the Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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Abstract

Introduction: Iclaprim, a dihydrofolate reductase inhibitor, completed two successful Phase 3 studies for the treatment of ABSSSI using a fixed dose of 80 mg infused over 2h. Here, key PK parameters of the fixed dose of iclaprim are compared to those of the weight-based dose used in two prior studies for complicated skin and skin structure infections.

Methods: The REVIVE-1/-2 Phase 3 studies were randomized, double-blind studies of iclaprim 80 mg fixed dose vs vancomycin 15 mg/kg, each infused over 2h Q12h for 5-14 days. The ASSIST-1 and -2 studies evaluated iclaprim 0.8 mg/kg weight-based dose vs linezolid 600 mg, each infused over 30 mins Q12h for 10-14 days. PK samples were obtained at Day 1, 48-72h post-initiation of dosing and end of treatment in the REVIVE studies and at Day 1 and 4 in the ASSIST studies. At those visits, samples pre-dose, 10 mins, 2h and 6h after iclaprim were obtained. The PK parameters including AUC, Cmax (parameter associated with safety in healthy volunteer studies), AUC/MIC and T> MIC (parameters associated with efficacy in animal infection models) were compared between the fixed and weight-based doses of iclaprim. The MIC_{90} of iclaprim for *Staphylococcus aureus* from global surveillance studies of 0.12 µg/mL was used for the calculations.

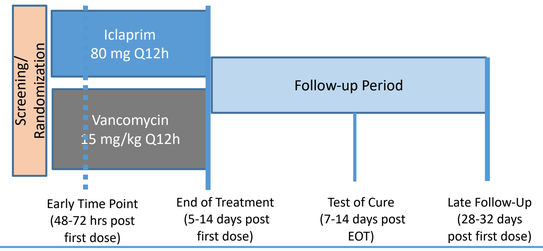
Results: Iclaprim PK parameters for the REVIVE and ASSIST studies are shown in Tables 2 and 3. For a target MIC of 0.12 µg/mL, the AUC/MIC and T>MIC were improved by 54% and 67%, respectively, with the fixed 2h dose compared to the weight-based 30 min dose. The Cmax was reduced by 7.3% with the fixed 2h dose compared to the weight-based 30 min dose. These differences are unlikely to be due solely to differences in subject populations as the distribution of age, the main covariate for iclaprim exposure, was very similar in the REVIVE and ASSIST studies.

Conclusions: Compared to the previous weight-based dosing regimen, the fixed dose of iclaprim 80 mg infused over 2h provides higher AUC/MIC and T>MIC (efficacy) and lower Cmax (safety) with an easier dosing regimen, and was effective in patients with skin and skin structure infections.

Introduction

- Iclaprim is a novel next generation diaminopyrimidine and is selective bacterial dihydrofolate reductase inhibitor.
  - Two identical Phase 3 randomized, double-blind, placebo-controlled studies met the primary endpoint of noninferiority (10% margin) of iclaprim 80 mg compared to vancomycin 15 mg/kg administered Q12h for 5-14 days for the treatment of ABSSSI (Figure 1).[1,2]
- Pharmacokinetic parameters of the 80 mg fixed dose of iclaprim are compared to those of the weight-based dose of 0.8 mg/kg used in two prior studies (ASSIST-1 and-2) for complicated skin and skin structure infections.

Figure 1. Study Design Diagram for the REVIVE-1 and REVIVE-2 Studies.



Methods

- Iclaprim pharmacokinetic data from the pooled REVIVE studies were compared with data from the pooled ASSIST studies.
  - REVIVE-1 and -2 studies evaluated iclaprim 80 mg fixed dose versus vancomycin 15 mg/kg; study drugs were infused over 2 hours Q12h for 5-14 days.
  - ASSIST-1 and -2 studies evaluated iclaprim 0.8 mg/kg weight-based dose versus linezolid 600 mg; study drugs were infused over 30 mins Q12h for 10-14 days.
- PK samples were obtained pre-dose, 10 mins, 2h and 6h after iclaprim during the following time points
  - REVIVE studies: Day 1, 48-72h post-initiation of dosing and end of treatment
  - ASSIST studies: Day 1 and 4
- A full model approach was used with concentration-time data modelled using NONMEM® (v7.3) and R (v3.3.3).
- Covariates
  - REVIVE studies: age, weight, gender, race, glomerular filtration rate (eGFR), and liver function
  - ASSIST studies: gender, ethnicity, age, weight, body mass index, total bilirubin, ALT level, creatinine clearance
- The PK parameters including AUC, Cmax (parameter associated with safety in healthy volunteer studies), AUC/MIC and T> MIC (parameters associated with efficacy in animal infection models) were compared between the fixed and weight-based doses of iclaprim.
  - The MIC_{90} of iclaprim for *Staphylococcus aureus* from global surveillance studies of 0.12 µg/mL was used for the calculations.

Results

- Pharmacokinetic samples were obtained from 589 iclaprim-treated patients in the REVIVE studies and 470 patients in the ASSIST studies (Table 1).
- Patients in both pooled studies had similar mean age of 48 years.

Results

- ALT levels were higher in patients in the pooled REVIVE studies with a mean of 31 U/L compared with 13 U/L in the pooled ASSIST studies.
  - 28% of patients in the pooled REVIVE studies had chronic hepatitis C infection.[1,2]

Table 1. Demographics and Baseline Characteristics of Patients who Received Iclaprim in the REVIVE and ASSIST Studies.

	REVIVE Studies Fixed 2h Dose (n=589)	ASSIST Studies Weight-based 30 min Dose (n=476*)
Age, years, mean (±SD)	48 (15)	48 (15)
Males, n (%)	378 (64)	308 (65)
White, n (%)	528 (90)	391 (82)
Weight, kg, mean (±SD)	82 (20)	79 (17)
Baseline ALT, U/L, mean (±SD)	31 (33)	13 (22)
Baseline eGFR, mL/min/1.73m², mean (±SD)	101 (28)	99 (29)**

*6 subjects had no Day 4 concentrations for PK parameters. **Creatinine clearance, mL/min.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate..

- Iclaprim PK parameters for the REVIVE and ASSIST studies are shown in Table 2.
- The population PK model indicates that patients in the REVIVE studies had a median AUC of 5924 h•ng/mL and a median Cmax of 651 ng/mL (mean Cmax of 687 ng/mL).
- The Cmax was reduced by 7.3% with the iclaprim 80 mg fixed dose infused over 2 hours compared to the 0.8 mg/kg weight-based dose infused over 30 minutes.

Table 2. PK parameters for the REVIVE and ASSIST studies.

	REVIVE Studies Fixed 2h Dose (n=589)	ASSIST Studies Weight-based 30 min Dose (n=470)
Median AUC (IQR), h•ng/mL	5924 (4367-7999)	3865 (2992-5394)
Median Cmax (IQR), ng/mL	651 (468-906)	702 (572-953)
Mean Volume of distribution (SD), L	121 (39.9)	125 (54)
Mean Clearance (SD), L/hr	31.0 (12.3)	34.0 (13.6)
Mean $T_{1/2}$ (SD), hr	3.39 (0.635)	4.61 (3.48)

Results

- For a target MIC of 0.12 µg/mL, the AUC/MIC and T>MIC were improved by 54% and 67%, respectively, with the iclaprim 80 fixed dose infused over 2 hours compared to the 0.8 mg/kg weight-based dose infused over 30 minutes (Table 3).

Table 3. PD parameters for the REVIVE and ASSIST studies.

	REVIVE Studies Fixed 2h Dose (n=589)	ASSIST Studies Weight-based 30 min Dose (n=470)
AUC/MIC (IQR), hr	49.4 (48.5-50.3)	32 (24-45)
T>MIC (IQR), %	65.3 (64.0-66.1)	39.2 (27.5-55.0)

- These differences in PK and PD parameters are unlikely to be due solely to differences in subject populations as the distribution of age, the main covariate for iclaprim exposure, was very similar in the REVIVE and ASSIST studies. These differences were likely due to changes in the dosing and infusion times.

Conclusions

- Compared to the previous weight-based dosing regimen, the fixed dose of iclaprim 80 mg infused over 2h provides higher AUC/MIC and T>MIC (efficacy) and lower Cmax (safety) with an easier dosing regimen. No dosage adjustment in obese patients or patients with renal impairment.
- Iclaprim was effective and safe in patients with acute bacterial skin and skin structure infections.

References

1. Huang DB, et al. *Clin Infect Dis* 2018;66:1222-1229.
2. Holland TL, et al. *Antimicrob Agents Chemother* 2018;62:e02580-17.

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