The Safety of Iclaprim among Diabetic Patients for the Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI): Pooled REVIVE Studies

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INTRODUCTION

- Diabetes is a risk factor for ABSSSI.
  - Patients with diabetes have worse outcomes with increased clinical failures and longer hospitalizations than patients without diabetes [1, 2].
- In two Phase 3 trials (REVIVE-1 and REVIVE-2) iclaprim has shown clinical response comparable to vancomycin among patients treated for ABSSSI [3,4].
- The objective of this post-hoc analysis was to determine the safety of iclaprim versus vancomycin in the treatment of ABSSSI among patients with diabetes.

METHODS

- A pooled analysis from two Phase 3, randomized, double-blind studies (REVIVE-1 and REVIVE-2) that evaluated the safety and efficacy of intravenous iclaprim versus vancomycin in the treatment of ABSSSI suspected or confirmed to be due to Gram-positive pathogens was conducted.
- All patients with diabetes were evaluated for safety on the basis of medical history and physical examinations, routine electrocardiography, laboratory tests, urinalysis and reports of clinical adverse events (AEs).
  - While blinded to treatment assignment, the investigator categorized the severity of each AE and the relationship to study drug.
- Baseline renal impairment was determined by Cockcroft-Gault formula.

RESULTS

- 11% (127/1198) of ITT patients in the REVIVE studies had diabetes.
  - Slightly more patients with diabetes were treated with vancomycin (n=71) than with iclaprim (n=56).
- Renal impairment was common among patients with diabetes in the pooled REVIVE ITT population.
  - Mild, or moderate to severe renal impairment was reported in 22/56 (39.2%) of diabetic patients in the iclaprim group and 26/71 (36.6%) in the vancomycin group. (Table 1).

Table 1. Baseline renal function of ABSSSI patients with diabetes (ITT population).

	REVIVE-1		REVIVE-2		Pooled REVIVE	
Creatinine Clearance, n (%)*	Iclaprim (n=20)	VAN (n=35)#	Iclaprim (n=36)#	VAN (n=36)	Iclaprim (n=56)#	VAN (n=71)#
≥ 90 ml/min	11 (55.0)	20 (57.1)	22 (61.1)	23 (63.8)	33 (58.9)	43 (60.5)
60-89 ml/min	8 (40.0)	7 (20.0)	8 (22.2)	8 (22.2)	16 (28.5)	15 (21.1)
15-59 ml/min	1 (5.0)	6 (17.1)	5 (13.8)	5 (13.8)	6 (10.7)	11 (15.4)

Abbreviations: VAN, vancomycin

*No patients had creatinine clearance <15 mL/min.

#Data on renal function is missing on 1 iclaprim-treated patient and 2 vancomycin-treated patients.

- Overall, AEs were numerically lower in the iclaprim group compared with the vancomycin group (Table 2).
- Three patients with diabetes who were treated with vancomycin developed acute kidney injury/increased blood creatinine levels, whereas no patients treated with iclaprim developed these renal AEs in the REVIVE studies.
- Discontinuation of study drug due to an AE was reported in 3.6% (2/56) of patients treated with iclaprim versus 10.0% (7/70) of patients treated with vancomycin.

RESULTS

Table 2. Adverse events among ABSSSI patients with diabetes (Safety population).

	REVIVE-1		REVIVE-2		Pooled REVIVE-1/2	
n (%)	Iclaprim (N=20)	VAN (N=34)	Iclaprim (N=36)	VAN (N=36)	Iclaprim (N=56)	VAN (N=70)
Deaths	0	1 (2.9)	0	0	0	1 (1.4)
Serious AEs	1 (5.0)	3 (8.8)	4 (11.1)	2 (5.6)	5 (8.9)	5 (7.1)
AEs leading to discontinuation	0	4 (11.8)	2 (5.6)	3 (8.3)	2 (3.6)	7 (10.0)
Drug-related AEs	2 (10.0)	7 (20.6)	3 (8.3)	4 (11.1)	5 (8.9)	11 (15.7)
Any AEs	7 (35.0)	19 (55.9)	20 (55.6)	18 (50.0)	27 (48.2)	37 (52.9)
Pyrexia	0	3 (8.8)	0	1 (2.8)	0	4 (5.7)
Phlebitis	0	0	2 (5.6)	1 (2.8)	2 (3.6)	1 (1.4)
Blood glucose increased*	0	0	0	1 (2.8)	0	1 (1.4)
Acute kidney injury/ Blood creatinine increased#	0	1 (2.9)	0	2 (5.6)	0	3 (4.3)
Hypo-magnesemia*	0	0	2 (5.6)	1 (2.8)	2 (3.6)	1 (1.4)
AST increased*	0	0	1 (2.8)	0	1 (1.8)	0
ALT increased*	0	0	1 (2.8)	1 (2.8)	1 (1.8)	1 (1.4)
QTc prolongation (QTcF >500 ms or >60 ms from BL)	0	0	0	0	0	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; ms, milliseconds; VAN, vancomycin.

*Investigator reported.

#Patients who have a confirmed increase in serum creatinine (SCr) of 0.5mg/dL from baseline, if SCr was normal at baseline or a 50% increase in SCr from baseline, if the upper limit of SCr was not normal at baseline.

CONCLUSIONS

- Renal impairment was common among patients with diabetes in the ITT population of the REVIVE studies (37.8%).
- Overall, there were numerically lower AEs in the diabetic patients treated with iclaprim (48.2%) compared with vancomycin (52.9%).
  - Lower numbers of treatment-related AEs were reported in those treated with iclaprim compared with vancomycin (8.9% vs 15.7%).
- Diabetic patients, particularly those with renal impairment, may be vulnerable to vancomycin related AEs, including nephrotoxicity.
- Further evaluation is warranted, given the frequent occurrence of diabetes among hospitalized ABSSSI patients, and the broad use of vancomycin in hospital settings.

REFERENCES

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