A Pooled Analysis of the Safety and Efficacy of Iclaprim Versus Vancomycin for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Patients With Intravenous Drug Use: Phase 3 REVIVE Studies

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ABSTRACT

Purpose: This analysis evaluates the efficacy and safety of iclaprim versus vancomycin for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in patients who were intravenous drug users (IVDUs).

Methods: A total of 621 patients who were IVDUs from 2 parallel Phase III, double-blind, randomized (1:1), active-controlled, multinational, multicenter trials (REVIVE-1 and REVIVE-2) were analyzed separately and pooled. This post hoc analysis summarizes the efficacy and safety profile of iclaprim 80 mg fixed dose compared with vancomycin 15 mg/kg administered intravenously during 2 h every 12 h for 5−14 days among this population. The primary end point of these studies was to determine whether iclaprim was noninferior (10% margin) to vancomycin in achieving a ≥20% reduction in lesion size at 48−72 h after initiation of treatment with the study drug (early clinical response) in the intent-to-treat population. The safety profile was assessed based on adverse events and laboratory parameters.

Findings: Iclaprim had higher early clinical response rates (85.8%; 95% CI, 81.5%−89.4%) compared with vancomycin (79.8%; 95% CI, 74.8%−84.2%) among patients with ABSSSIs who were IVDUs, with a treatment difference of +6.00% (95% CI, 0.06−12.0). The safety profile was similar in the iclaprim and vancomycin arms, with 3.7% and 5.0%, respectively, of patients discontinuing study therapy because of adverse events and 1.9% and 3.4%, respectively, of patients developing serious adverse events.

Implications: Iclaprim had a higher early clinical response rate and favorable safety profile compared with vancomycin for the treatment of ABSSSIs in patients who were IVDUs. Iclaprim may be a valuable treatment option for ABSSSIs in this patient population. (*Clin Ther*. 2019;41:1090−1096) © 2019 Published by Elsevier Inc.

Keywords: iclaprim, skin infection, intravenous drug use, vancomycin.

INTRODUCTION

In 2017, the US Department of Health and Human Services declared the US opioid epidemic a public health emergency.[1] A total of 11.4 million people misused prescription opioids, and 2.1 million people had an opioid use disorder.[1] Of these, >130 people die every day of opioid-related drug overdoses, with a total of 47,600 people dying annually from opioid overdose.[1]

Acute bacteria skin and structure infections (ABSSSIs) are the most common cause of hospital admission of intravenous drug users (IVDUs). Injecting illicit drugs exposes the user to an increased risk of acquiring various infections along with the

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transmission of certain chronic bloodborne infections. In the United States, *Staphylococcus aureus* has been the predominant causative pathogen of ABSSSIs, with approximately 50% of cases being methicillin-resistant *S aureus* (MRSA).[2]

Iclaprim is a diaminopyrimidine antibiotic that selectively inhibits bacterial dihydrofolate reductase and is active against gram-positive pathogens, including MRSA.[3,4] Iclaprim is in the same class as trimethoprim, the only dihydrofolate reductase inhibitor approved the US Food and Drug Administration, and was designed to be more potent than trimethoprim, overcoming select trimethoprim resistance among gram-positive pathogens.[5] In addition, unlike trimethoprim, iclaprim does not need to be combined with a sulfonamide, which is commonly associated with adverse events, including renal toxic effects, hepatotoxic effects, blood dyscrasias, anaphylaxis, and hypersensitivity reactions.[6]

Two identical Phase III randomized, double-blind, placebo-controlled studies (REVIVE-1 and REVIVE-2) were conducted to evaluate iclaprim 80 mg fixed dose compared with vancomycin 15 mg/kg, both infused during 2 h and administered every 12 h for 5−14 days to patients with ABSSSIs.[7,8] A post hoc analysis was conducted to evaluate the efficacy and safety data from the pooled REVIVE-1 and REVIVE-2 studies for the subset of patients with ABSSSIs who were IVDUs.

MATERIALS AND METHODS

Overall, 1198 patients were included in the intent-to-treat (ITT) populations in the REVIVE-1 (n = 598) and REVIVE-2 (n = 600) ABSSSI Phase III clinical studies. These Phase III studies have been described previously.[7,8] In brief, both the REVIVE-1 and REVIVE-2 studies were 600-patient, double-blinded, randomized (1:1), active-controlled trials among patients with ABSSSIs that compared iclaprim 80 mg fixed dose with vancomycin 15 mg/kg (adjusted for renal function), both administered intravenously during 2 h every 12 h for 5−14 days, according to the investigator assessment of clinical response. The median duration of treatment was 7 days (range, 1−15 days) for the iclaprim and vancomycin groups. The primary objective of each of these Phase III studies was to demonstrate whether iclaprim was noninferior to vancomycin in achieving ≥20% reduction in lesion size at 48−72 h after initiation of study drug (early clinical response at the early time point) in the ITT population. The noninferiority test was a 1-sided hypothesis test performed at the 2.5% level of significance and was based on the lower limit of the 2-sided 95% CI. The noninferiority bound was prespecified as 10%. Equivalently, if the lower bound of the 2-sided 95% CI for the difference between the 2 treatment proportions was >−0.100 based on the z test with unpooled variance estimate, then noninferiority of iclaprim to vancomycin was declared.

Per protocol, ABSSSIs (major abscesses, cellulitis, or wound infections) were defined as having purulent or seropurulent drainage before or after surgical intervention of the wound or at least 3 of the following signs and symptoms: discharge, erythema (extending at least 2 cm beyond the wound edge in any direction), swelling and/or induration, heat and/or localized warmth, and/or pain and/or tenderness to palpation. Patients with known or suspected gram-negative ABSSSIs were excluded. The data were analyzed separately in the REVIVE-1 and REVIVE-2 studies and then pooled to determine the efficacy and safety of the iclaprim and vancomycin arms in this subset of patients who were IVDUs. Intravenous drug use was defined based on medical history of the patient.

At the baseline visit, ABSSSIs were sampled for microbiological culture. Cultures were performed locally, and isolates were submitted to the central microbiology laboratory. Antibacterial susceptibility testing was conducted by International Health Management Associates Europe Sàrl Laboratories (Monthey, Switzerland). Susceptibility testing was performed by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines M07-A10[9] and the standard operating procedures at the International Health Management Associates laboratories. Quality controls and interpretation of results were performed in accordance with CLSI M100.[10]

RESULTS

Of the 621 patients treated in the pooled REVIVE-1 and REVIVE-2 studies with ABSSSIs who were IVDUs, 324 (52%) were treated with iclaprim and 297 (48%) with vancomycin. Similar demographic and baseline characteristics were observed in the iclaprim and vancomycin groups in the ITT population (Table I). The mean (SD) lesion size of the

Table I. Demographic and baseline characteristics of patients with ABSSSIs who were IVDUs.*

Characteristic	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim (n = 187)	Vancomycin (n = 148)	Iclaprim (n = 137)	Vancomycin (n = 149)	Iclaprim (n = 324)	Vancomycin (n = 297)
Age, mean (SD), y	44.6 (11.85)	44.0 (11.32)	43.8 (10.98)	45.1 (11.81)	44.2 (11.48)	44.5 (11.56)
Male	130 (69.5)	89 (60.1)	93 (67.9)	108 (72.5)	223 (68.8)	197 (66.3)
Race						
White	170 (90.9)	138 (93.2)	129 (94.2)	129 (86.6)	299 (92.3)	267 (89.9)
Black	3 (1.6)	5 (3.4)	3 (2.2)	8 (5.4)	6 (1.9)	13 (4.4)
Other	14 (7.5)	5 (3.4)	5 (3.6)	12 (8.1)	19 (5.9)	17 (5.7)
Lesion size, mean (SD), cm^2	318.2 (278.84)	327.2 (303.31)	330.1 (216.63)	314.7 (211.30)	323.2 (254.10)	320.9 (260.86)
Comorbidities						
Diabetes	5 (2.7)	9 (6.1)	3 (2.2)	8 (5.4)	8 (2.5)	17 (5.7)
Creatinine clearance, mL/min						
≥90	172 (92.0)	129 (87.2)	121 (88.3)	132 (88.6)	293 (90.4)	261 (87.9)
60—<90	13 (7.0)	15 (10.1)	14 (10.2)	15 (10.1)	27 (8.3)	30 (10.1)
15—<60	0	2 (1.4)	2 (1.5)	2 (1.3)	2 (0.6)	4 (1.3)
Geographic region						
United States	187 (100.0)	148 (100.0)	137 (100.0)	149 (100.0)	324 (100.0)	297 (100.0)
Europe	0	0	0	0	0	0
Latin America	0	0	0	0	0	0
Bacteremia	7 (3.7)	7 (4.7)	2 (1.5)	8 (5.4)	9 (2.8)	15 (5.1)
Coadministration of aztreonam	6 (3.2)	7 (4.7)	11 (8.0)	13 (8.7)	17 (5.2)	20 (6.7)
Coadministration of metronidazole	1 (0.5)	1 (0.7)	3 (2.2)	6 (4.0)	4 (1.2)	7 (2.4)

ABSSSIs = acute bacterial skin and skin structure infections; IVDUs = intravenous drug users.
* Data are presented as number (percentage) of patients unless otherwise indicated.

ABSSSIs was approximately 323.2 (254.1) cm^2 and 320.9 (260.9) cm^2 among patients treated with iclaprim and vancomycin, respectively.

Table II gives the microbiological findings from the subpopulation of IVDUs with available isolates. The most common pathogen was *S aureus*, occurring in 193 of 324 patients (59.6%) treated with iclaprim and 178 of 297 patients (59.9%) treated with vancomycin. MRSA accounted for 105 of 324 ABSSSIs (32.4%) in patients treated with iclaprim and 89 of 297 ABSSSIs (30.0%) in patients treated with vancomycin and in 54.4% and 50.0% of *S. aureus* isolates cultured from patients with ABSSSIs treated with iclaprim and vancomycin, respectively. Other bacteria cultured from ABSSSIs include *Streptococcus anginosus*, *Streptococcus agalactiae,* and *Streptococcus pyogenes*. Nine patients (2.8%) treated with iclaprim and 15 patients (5.1%) treated with vancomycin had positive blood culture results.

The iclaprim group had an early clinical response rate of 85.8% (95% CI, 81.5%−89.4%) compared with 79.8% (95% CI, 74.8%−84.2%) in the vancomycin group among the subset of patients with ABSSSIs who were IVDUs in the ITT analysis of the pooled trials (Table III). The treatment difference was +6.00% (95% CI, 0.06%−11.95%. End-of-treatment response rates were 92.3% and 88.9% in the iclaprim and vancomycin groups, respectively, and clinical cure rates at the test-of-cure visit (7−14 days after the end of treatment) were similar between the 2 groups (83.3% in the iclaprim group compared with 83.8% in the vancomycin group).

Among the patients with ABSSSIs who were IVDUs and had bacteria identified from their infections, the MIC_{50}/MIC_{90} against all *S aureus* isolates were 0.06/0.12 μg/mL for iclaprim and 0.06/0.12 μg/mL for vancomycin; MIC_{50}/MIC_{90} values against MRSA were 0.03/0.25 μg/mL for iclaprim and 0.03/>8 μg/mL for vancomycin.

Iclaprim and vancomycin had similar adverse event profiles in patients who were IVDUs (Table IV). Adverse events leading to discontinuation of study therapy occurred in 12 of 323 (3.7%) of the iclaprim-treated patients and in 15 of 298 (5.0%) of those treated with vancomycin. Approximately 20% of patients experienced an adverse event during the study; of these, the most common in both treatment groups were nausea and headache. Study drug−related adverse events were reported in 22.0% and 18.1% of patients in the iclaprim and vancomycin groups, respectively. Notable differences in adverse events during the study included nausea in 38 of 323 patients (11.8%) given iclaprim compared

Table II. Microbiological findings at baseline for patients with ABSSSIs who were IVDUs.*

Finding	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim (n = 187)	Vancomycin (n = 148)	Iclaprim (n = 137)	Vancomycin (n = 149)	Iclaprim (n = 324)	Vancomycin (n = 297)
Staphylococcus aureus	114 (61.0)	90 (60.8)	79 (57.7)	88 (59.1)	193 (59.6)	178 (59.9)
MRSA	61 (32.6)	40 (27.0)	44 (32.1)	49 (32.9)	105 (32.4)	89 (30.0)
MSSA	53 (28.3)	50 (33.8)	36 (26.3)	39 (26.2)	89 (27.5)	89 (30.0)
Staphylococcus pyogenes	14 (7.5)	7 (4.7)	6 (4.4)	5 (3.4)	20 (6.2)	12 (4.0)
Streptococcus agalactiae	1 (0.5)	0	0	0	1 (0.3)	0
Streptococcus anginosus group	29 (15.5)	22 (14.9)	29 (21.2)	27 (18.1)	58 (17.9)	49 (16.5)

ABSSSIs = acute bacterial skin and skin structure infections; IVDUs = intravenous drug users; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

* Percentages do not total 100% because some patients had >1 pathogen identified from their ABSSSI.

Table III. Early clinical response at the early time point for patients with ABSSSIs who were IVDUs.*

Study	No. (%) of Patients [95% CI]†	Difference (95% CI), %†,‡
REVIVE-1		
Iclaprim	158 (84.5) [78.5–89.4]	4.76 (–3.54 to 13.06)
Vancomycin	118 (79.7) [72.3–85.9]	
REVIVE-2		
Iclaprim	120 (87.6) [80.9–92.6]	7.73 (–0.76 to 16.21)
Vancomycin	119 (79.9) [72.5–86.0]	
Combined REVIVE-1 and REVIVE-2		
Iclaprim	278 (85.8) [81.5–89.4]	6.00 (0.06 to 11.95)
Vancomycin	237 (79.8) [74.8–84.2]	

ABSSSIs = acute bacterial skin and skin structure infections; IVDUs = intravenous drug users.
* The denominator for percentages is the number of patients in the intent-to-treat population for each treatment group.
† Early clinical response is defined as ≥20% reduction in lesion size at early time point (ETP) compared with baseline.
‡ The 2-sided 95% CI is based on the exact binomial CI for the proportions of the 2 groups and is based on the *z* test with unpolled variance estimate for the difference in the 2 proportions. If the lower bound of the 95% CI is >–0.10, noninferiority is concluded.

Table IV. Treatment-emergent safety profile in patients with ABSSSIs who were IVDUs.

Safety Parameter	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim (n = 180)	Vancomycin (n = 157)	Iclaprim (n = 127)	Vancomycin (n = 133)	Iclaprim (n = 307)	Vancomycin (n = 290)
Death	0	1 (0.7)	0	0	0	1 (0.3)
Serious AEs	5 (2.7)	7 (4.7)	1 (0.7)	3 (2.0)	6 (1.9)	10 (3.4)
AEs leading to discontinuation	6 (3.2)	8 (5.4)	6 (4.4)	7 (4.7)	12 (3.7)	15 (5.0)
Any AE	123 (65.8)	84 (56.8)	65 (47.8)	60 (40.0)	188 (58.2)	144 (48.3)
Drug-related AEs	52 (27.8)	40 (27.0)	19 (14.0)	14 (9.3)	71 (22.0)	54 (18.1)
Most common AEs (>5%)	90 (48.1)	54 (36.5)	38 (27.9)	30 (20.0)	128 (39.6)	84 (28.2)
Nausea	27 (14.4)	15 (10.1)	11 (8.1)	8 (5.3)	38 (11.8)	23 (7.7)
Headache	28 (15.0)	21 (14.2)	5 (3.7)	8 (5.3)	33 (10.2)	29 (9.7)
Infusion site extravasation	13 (7.0)	11 (7.4)	11 (8.1)	8 (5.3)	24 (7.4)	19 (6.4)
Vomiting	14 (7.5)	12 (8.1)	5 (3.7)	5 (3.3)	19 (5.9)	17 (5.7)
Fatigue	17 (9.1)	8 (5.4)	0	1 (0.7)	17 (5.3)	9 (3.0)

ABSSSIs = acute bacterial skin and skin structure infections; AE = adverse effect; IVDUs = intravenous drug users.

with 23 of 298 patients (7.7%) treated with vancomycin and fatigue in 17 of 323 patients (5.3%) given iclaprim vs 9 of 298 patients (3.0%) given vancomycin.

DISCUSSION

In this post hoc analysis of the 2 Phase III REVIVE studies, iclaprim achieved higher early clinical response compared with vancomycin in patients with

ABSSSIs who were IVDUs (86% vs 80%) even though the clinical cure rate at end of treatment and test-of-cure visit were similar. A possible explanation for the numerically higher early clinical response at the early time point for iclaprim compared with vancomycin is that iclaprim suppresses *S aureus* toxins of Panton-Valentine leukocidin, α-hemolysin, and toxic-shock syndrome toxin I in MRSA and vancomycin-intermediate *S aureus*, thereby allowing the host immune system to clear the pathogen and resolving ABSSSI signs and symptoms that may be caused by the bacterial exotoxin.[11] In contrast, vancomycin lacks the ability to interfere with toxin production by *S aureus* in the setting of tissue invasion.

There were similarities and differences between patients with ABSSSI who were and were not IVDUs. The mean lesion size for ABSSSI was similar in patients who were or were not IVDUs (320 vs 350 cm^2).[12] Although some ABSSSIs may be treated with topical (if minor) or oral antibacterial agents, the mean lesion size of the ABSSSI in the REVIVE trials[12] was approximately 300 cm^2, which is substantial and commensurate with a need for intravenous therapy. In addition, IVDUs may be less adherent with use of topical or oral antibacterial agents, which may lead to increased selective pressure from nonadherence with the duration of outpatient treatment. In these analyses, 3% to 5% of patients had bacteremia, for which intravenous antibiotics are required. The gram-positive pathogens, including *S aureus*, associated with ABSSSIs in patients who were IVDUs were similar to those resulting in abscesses and wound infections in the pooled REVIVE studies.[12] A difference between the patients who were and were not IVDUs was the second most commonly identified pathogen at baseline in the *S anginosus* group, identified in approximately 17% of patients who were IVDUs compared with approximately <5% who were not IVDUs. This difference may be explained by the high rate of illicit drug users, who may lick their needles before injecting themselves, contaminating the needles with oral flora, such as *S anginosus*. The $MIC_{50/90}$ against *S anginosus* isolates (n = 113) was ≤0.004/0.008 for iclaprim and 1/1 for vancomycin.

In conclusion, iclaprim had a higher early clinical response rate and a favorable safety profile compared with vancomycin in the treatment of ABSSSIs in patients who were IVDUs. Iclaprim may be a valuable treatment option for these patients with ABSSSIs suspected or confirmed to be attributable to gram-positive pathogens.

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REFERENCES

1. US Department of Health and Human Services. What Is the US opioid epidemic? https://www.hhs.gov/opioids/about-the-epidemic/index.html.
2. Ray GT, Suaya JA, Baxter R. Microbiology of skin and soft tissue infections in the age of community-acquired methicillin-resistant *Staphylococcus aureus*. *Diagn Microbiol Infect Dis*. 2013;76:24–30.
3. Sader HS, Fritsche TR, Jones RN. Potency and bactericidal activity of iclaprim against recent clinical gram-positive isolates. *Antimicrob Agents Chemother*. 2009;53:2171–2175.
4. Schneider P, Hawser S, Islam K. Iclaprim, a novel diaminopyrimidine with potent activity on trimethoprim sensitive and resistant bacteria. *Bioorg Med Chem Lett*. 2003;13:4217–4221.

5. Oefner C, Bandera M, Haldimann A, et al. Increased hydrophobic interactions of iclaprim with *Staphylococcus aureus* dihydrofolate reductase are responsible for the increase in affinity and antibacterial activity. *J Antimicrob Chemother*. 2009;63:687–698.
6. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. *CMAJ*. 2011;183:1851–1858.
7. Huang DB, O'Riordan W, Overcash JS, et al. A phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin for the treatment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens: REVIVE-1. *Clin Infect Dis*. 2018;66:1222–1229.
8. Holland TL, O'Riordan W, McManus A, et al. A phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin for treatment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens (REVIVE-2 Study). *Antimicrob Agents Chemother*. 2018;62.e02580–17.
9. M07-A10 CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard*. 10th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
10. M100 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing: 27th Informational Supplement*. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.
11. Bryant AE, Gomi S, Katahira E, et al. The effects of iclaprim on exotoxin production in methicillin-resistant and vancomycin-intermediate Staphylococcus aureus. *J Med Microbiol*. 2019;68:456–466.
12. Huang DB, Corey GR, Holland TL, et al. Pooled analysis of the phase 3 REVIVE trials: randomised, double-blind studies to evaluate the safety and efficacy of iclaprim versus vancomycin for treatment of acute bacterial skin and skin-structure infections. *Int J Antimicrob Agents*. 2018;52:233–240.

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