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A Pooled Analysis of Patients with Wound Infections in the Phase 3 REVIVE Trials: Randomized, Double-blind Studies to EValuate the Safety and Efficacy of Iclaprim Versus Vancomycin for trEatment of Acute Bacterial Skin and Skin Structure Infections

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Abstract

Introduction: Iclaprim is a diaminopyrimidine antibiotic for the treatment of acute bacterial skin and skin structure infections (ABSSSI) due to Gram-positive pathogens.

Aim: This analysis evaluates patients with wound infections from two Phase 3 trials of ABSSSI.

Methodology: Six-hundred-two patients with wound infections from two phase 3, double-blinded, randomized, multicenter, active controlled trials (REVIVE-1/-2) were evaluated in a post-hoc analysis of iclaprim 80 mg compared with vancomycin 15 mg/kg administered intravenously every 12 hours for 5-14 days. The primary endpoint was to determine whether iclaprim was non-inferior (10% margin) to vancomycin in achieving a ≥20% reduction from baseline in lesion size 48-72 hours after starting study drug (early clinical response [ECR]). Safety was assessed.

Results: In REVIVE-1, ECR was 83.5% with iclaprim versus 79.7% with vancomycin (treatment difference 3.77%, 95% CI -4.50%, 12.04%). In REVIVE-2, ECR was 82.7% with iclaprim versus 76.3% with vancomycin (treatment difference 6.38%, 95% CI -3.35%, 16.12%). In the pooled dataset, iclaprim had similar ECR rates compared with vancomycin among wound infection patients (83.2% vs 78.2%) with a treatment difference of 5.01% (95% CI -1.29%, 11.32%). The safety profile was similar in iclaprim- and vancomycin-treated patients, except for a higher incidence of diarrhea with vancomycin (n=17) compared with iclaprim (n=6) and fatigue with iclaprim (n=17) compared with vancomycin (n=8).

Conclusion: Based on early clinical response, iclaprim achieved non-inferiority to vancomycin

with a similar safety profile in patients with wound infections suspected or confirmed as caused by Gram-positive pathogens. Iclaprim may be a valuable treatment option for wound infections.

Keywords: iclaprim, wound infection, Gram-positive

Introduction

Wound infections may occur through a break in the skin when bacteria enter and attach to the tissues so that the normal wound healing process is interrupted [1]. Wound infections can be post-traumatic occurring due to lacerations, burns, bites and punctures (including intravenous drug use) or post-surgical. Data on the incidence of wound infections (both post-traumatic and post-surgical) underestimate the true incidence because most wound infections occur in the community without hospital reporting. In the United States, Staphylococcus aureus has been the predominant causative pathogen of wound infections with approximately 50% methicillin-resistance (MRSA) [2].

Iclaprim is a diaminopyrimidine antibiotic, which 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 FDA approved dihydrofolate reductase inhibitor, and was designed to be more active than trimethoprim and to overcome 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 toxicity, hepatotoxicity, blood dyscrasias, anaphylaxis, and hypersensitivity reactions [6].

Two identical Phase 3 randomized, double-blind, active-controlled studies (REVIVE-1 and REVIVE-2) were conducted to evaluate iclaprim 80 mg fixed dose compared with vancomycin 15 mg/kg, both infused over 2 hours, administered every 12 hours to patients with ABSSSI [7,8]. Iclaprim achieved noninferiority (10% margin) compared to vancomycin for early clinical response at the early time point in both of these Phase 3 studies. A post-hoc analysis was

conducted to evaluate the efficacy and safety data from the pooled REVIVE-1 and -2 studies for the subset of patients treated for wound infections.

Materials and Methods

Overall, 1198 patients were included in the intent-to-treat populations in the REVIVE-1 (n=598) and REVIVE-2 (n=600) ABSSSI Phase 3 clinical trials. These Phase 3 studies have been described previously [7,8]. In brief, both REVIVE-1 and REVIVE-2 studies were 600-patient, phase 3, double-blinded, randomized (1:1), multi-center, active-controlled trials, non-inferiority studies that utilized identical study protocols (NCT02600611 and NCT02607618, respectively) among patients with ABSSSI that compared iclaprim 80 mg fixed dose with vancomycin 15 mg/kg (adjusted for renal function), both administered intravenously every 12 hours for 5-14 days, according to the investigator assessment of clinical response. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) guidance on trials for ABSSSI were incorporated into the study design. Patients were enrolled between March 2016 and January 2017 for REVIVE-1 [7] and between January 2016 and August 2017 for REVIVE-2 [8]. The median duration of treatment was 7 days (range: 1-15 days) for both the iclaprim and vancomycin groups. The primary objective of each of these Phase 3 studies was to demonstrate whether iclaprim was non-inferior to vancomycin in achieving $\geqslant$20% reduction in lesion size at 48 to 72 hours after initiation of study drug (early time point) in the intent-to-treat population. The non-inferiority margin was prespecified as 10%. Study protocols and informed consent forms were reviewed and approved by an institutional review board at each study site, and all patients or their authorized representative provided written informed consent prior to any study-specific procedures.

Cases of wound infections were pooled from the REVIVE studies based on the clinicians assessment and assignment of the ABSSSI as a wound infection prior to treatment randomization. Per protocol, wound infections were defined as having been caused by external trauma (e.g., needle sticks or insect bites) and had either the presence of 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. Disposition of patients in the pooled REVIVE-1 and REVIVE-2 studies are shown in **Figure 1**. The data were analyzed separately in the REVIVE-1 and -2 studies and then pooled to determine the efficacy and safety of the iclaprim and vancomycin arms in this subset of patients. Safety was assessed based on treatment-emergent adverse events (AEs), clinical laboratory tests (clinical chemistry, coagulation, hematology, liver function tests), urinalysis, vital signs, physical examinations and electrocardiograms (ECGs). The pooled analysis adds larger numbers (i.e., power) and confidence to the interpretation of secondary endpoints and the safety, especially where numbers were relatively small for specific secondary endpoints and potentially serious adverse events in the individual trials, among patients treated with iclaprim compared to vancomycin.

At the baseline visit, wound infections were sampled for microbiological culture. Cultures were performed locally, and isolates were submitted to the central microbiology laboratory. Antibacterial susceptibility testing was conducted by IHMA 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 IHMA laboratories. Quality controls and interpretation of results were performed in accordance with CLSI M100 [10].

Ethical Approval

The institutional review board at each site approved the protocol (for a list of the sites, see ClinicalTrials.gov NCT02600611 and NCT02607618), and all patients or their authorized representative provided written informed consent.

Results

Of the 602 patients treated in the pooled REVIVE-1 and -2 studies with wound infections, 51% (309/602) were treated with iclaprim and 49% (293/602) with vancomycin. Similar demographics and baseline characteristics were observed in the iclaprim and vancomycin groups in the intent to treat population; 69% of patients were male, mean age was approximately 46 years old, and 91% were white (**Table 1**). A high proportion of patients with wound infections were intravenous drug users (86% in the iclaprim arm and 82% in the vancomycin arm).

The mean lesion size of the wound infections was approximately 307 cm^2 and in the subpopulation with available isolates, the most common pathogen was S. aureus (72%; 363/505) (**Table 2**). In both treatment arms, MRSA accounted for 49% (177/363) of S. aureus isolates in wound infections. Streptococcus anginosus group pathogens constituted 21% (106/505) of isolates, and Streptococcus pyogenes 6% (32/505) of isolates. Seven (2%) patients treated with iclaprim and 18 (6%) patients treated with vancomycin had positive blood cultures.

The iclaprim group had a clinical response rate of 83.2% (95% CI 78.5, 87.2) at the early time point compared with 78.2% (95% CI 73.0, 82.8) in the vancomycin group among the subset of patients with wound infections in the intent-to-treat analysis of the pooled trials (**Figure 2**). The treatment difference was +5.01% with 95% confidence interval of -1.29% to 11.32%, thereby iclaprim established noninferiority to vancomycin in this subgroup of patients. End of treatment (EOT) response rates were 92.6% and 89.1% in the iclaprim and vancomycin groups, respectively, and clinical cure rates at the test-of-cure (TOC, 7-14 days after the end of treatment) were similar between the two groups (84.8% in the iclaprim group compared with 84.3% in the vancomycin group).

In patients with available isolates, the EOT and TOC response rates were 93.9% and 86.3%, respectively, in the pooled iclaprim arms compared with 91.7% and 88.4%, respectively, in the vancomycin arms. The MIC_{50}/MIC_{90} for iclaprim were 0.06/0.12 µg/mL and for vancomycin were 1/1 µg/mL against S. aureus isolates; MIC_{50}/MIC_{90} values against MRSA were 0.03/0.12 µg/mL for iclaprim and 1/1 µg/mL for vancomycin. Among patients with treatment failures, nearly 80% of pathogens from the culture of the wound infections had an iclaprim MIC of 0.03 or 0.06 µg/ml. The treatment success rate was not different between those that had single (iclaprim 83.6% and vancomycin 78.4%) compared to multiple pathogens identified from wound infections (iclaprim 83.1% and vancomycin 78.1%).

Iclaprim and vancomycin had similar adverse event profiles in patients with wound infections (**Table 3**). Adverse events leading to discontinuation of study therapy occurred in 2% of the iclaprim-treated patients and in 5% of those treated with vancomycin. Approximately 50-54% 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 21% and 19% of patients in the iclaprim and vancomycin groups, respectively. Notable differences in adverse events during the study included diarrhea in 2% (N=6) of patients given iclaprim compared with 6% (N=17) of patients treated with vancomycin, and fatigue in 6% (N=17) versus 3% (N=8) of patients receiving iclaprim or vancomycin, respectively. One patient treated with iclaprim experienced asymptomatic QTcF prolongation to 503 msec (Day1 preinfusion QTcF 429 msec).

Discussion

In this post-hoc analysis of the two Phase 3 REVIVE studies, iclaprim achieved non-inferiority to vancomycin in patients with wound infections, based on clinical response at the early time point. In the Phase 3 REVIVE studies, patients with wound infections were a majority of those enrolled and treated for ABSSSIs.

While some wound infections may be treated with either topical (if minor) or oral antibacterial agents, the mean lesion size of the ABSSSI in the REVIVE trials was approximately 300 cm^2, which is substantial and commensurate with a need for intravenous therapy. Additionally, some patients do not have good oral antibacterial options because of variable bioavailability, resistant bacteria or toxicity. In the REVIVE studies, between 2-6% of patients had bacteremia, for which intravenous antibiotics are appropriate.

The most commonly identified pathogen at baseline from the wound infections was S. aureus (72% in both treatment groups). Of the S. aureus, approximately 50% were MRSA in both treatment groups. The next most commonly identified pathogen at baseline from the wound infections were S. anginosus group (approximately 20% in both treatment groups). This may be

explained by the high rate of illicit drug users, who may lick their needles before injecting themselves, contaminating them with oral flora such as S. anginosus.

The ECR of 83% among patients with wound infections treated with iclaprim in the pooled REVIVE studies is similar to that observed with vancomycin in these studies (78%) and is consistent with similar studies in patients with wound infections treated with other currently used antibiotics. In the ESTABLISH-1 Phase 3 study, tedizolid was compared with linezolid in patients with ABSSSI [11]. Among patients with wound infections, the early clinical response rates were 86% in the tedizolid arm and 84% in the linezolid arm. Similar rates were observed in the identical study, ESTABLISH-2 [12]. In the OASIS-1 and OASIS-2 Phase 3 studies, omadacycline was compared with linezolid in patients with ABSSSI. Among patients with wound infection, the early clinical response rates were 84% in the omadacycline arm and 80% in the linezolid arm [13]. In the Phase 3 studies of delafloxacin compared with vancomycin plus aztreonam in patients with ABSSSI, among patients with wound infection, the early clinical response rates in the two studies were 78% and 84% in the delafloxacin arms and 81% in both of the vancomycin/aztreonam arms, respectively [14].

In the pooled REVIVE studies, there were several differences in the characteristics of the wound infections as well as the underlying patient comorbidities compared with cellulitis and/or abscesses [15]. The mean lesion size for wound infections was smaller than those for cellulitis/abscesses (307 cm^2 vs 390 cm^2). In addition, patients with wound infections were slightly younger with a mean age of 46 years in both arms compared with 52 years in the remaining population studied. Less of the population with wound infections also had diabetes and renal impairment compared with those with cellulitis/abscesses (diabetes: 7% vs 14%;

CrCl<90mL/min: 12% vs 24%), although a higher percentage of patients with wound infections were intravenous drug users (84% vs 20%).

The limitations of this analysis include that this is a post hoc analysis, although the sample size in this subpopulation was quite robust and represented approximately half of the patient populations in each treatment arm in both studies. Another limitation is the lack of reporting of types of wound infection, such as surgical site infections, and whether different types of wound infection influence surgical and antimicrobial outcomes by treatment with iclaprim or vancomycin. Nevertheless, these analyses provide important data on the outcomes of patients collectively with wound infections.

In conclusion, iclaprim was non-inferior to vancomycin in the treatment of patients with Gram-positive wound infections with a favorable safety profile. Iclaprim may be a valuable treatment option for patients with wound infections suspected or confirmed to be due to Gram-positive pathogens.

Source of Funding and Conflict of Interest

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Table 1. Demographics and baseline characteristics of patients with wound infections.

Characteristics	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim	Vancomycin	Iclaprim	Vancomycin	Iclaprim	Vancomycin
	(n=182)	(n=158)	(n=127)	(n=135)	(n=309)	(n=293)
Age, years, mean (SD)	45.0 (12.0)	45.2 (12.0)	47.8 (12.8)	46.2 (13.3)	46.1 (12.4)	45.7 (12.6)
Male, n (%)	127 (69.8)	100 (63.3)	86 (67.7)	101 (74.8)	213 (68.9)	201 (68.6)
Race, n (%) White Black Other	 165 (90.7) 3 (1.6) 14 (7.7)	 148 (93.7) 3 (1.9) 7 (4.4)	 117 (92.1) 3 (2.4) 7 (5.5)	 116 (85.9) 8 (5.9) 11 (8.1)	 282 (91.3) 6 (1.9) 21 (6.8)	 264 (90.1) 11 (3.8) 18 (6.1)
Lesion Size, cm^2, mean (SD)	302 (256)	315 (278)	314 (222)	299 (203)	307 (242)	308 (247)
Diabetes, n (%)	5 (3)	13 (8)	10 (8)	14 (10)	15 (5)	27 (9)
Creatinine clearance, n (%) ≥90 ml/min 60 - <90 ml/min 15 - <60 ml/min	 163 (91.6) 14 (7.9) 1 (0.6)	 136 (88.3) 15 (9.7) 3 (1.9)	 108 (85.0) 17 (13.4) 2 (1.6)	 115 (86.5) 14 (10.5) 4 (3.0)	 271 (88.9) 31 (10.2) 3 (1.0)	 251 (87.5) 29 (10.1) 7 (2.4)
Intravenous drug use, n (%)	170 (93)	134 (85)	95 (75)	106 (79)	265 (86)	240 (82)
Geographic region, n (%) United States Europe Latin America	 176 (96.7) 6 (3.3) 0	 148 (93.7) 10 (6.3) 0	 113 (89.0) 14 (11.) 0	 122 (90.4) 12 (8.9) 1 (0.7)	 289 (93.5) 20 (6.5) 0	 270 (92.2) 22 (7.5) 1 (0.3)
Bacteremia, n (%)	7 (3.8)	9 (5.7)	0	9 (6.7)	7 (2.3)	18 (6.1)
Co-administration of aztreonam, n (%)	6 (3.3)	7 (4.4)	12 (9.4)	13 (9.6)	18 (5.8)	20 (6.8)
Co-administration of metronidazole, n (%)	1 (0.5)	1 (0.6)	5 (3.9)	6 (4.4)	6 (1.9)	7 (2.4)

Table 2. Microbiological findings at baseline for patients with wound infections in the REVIVE studies.

Baseline Microbiology, n (%)	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim	Vancomycin	Iclaprim	Vancomycin	Iclaprim	Vancomycin
	(n=151)	(n=128)	(n=112)	(n=114)	(n=263)	(n=242)
S. aureus	115 (76.2)	98 (76.6)	74 (66.1)	76 (66.7)	189 (71.9)	174 (71.9)
MRSA	56 (37.1)	39 (30.5)	39 (34.8)	43 (37.7)	95 (36.1)	82 (33.9)
MSSA	59 (39.1)	59 (46.1)	36 (32.1)	33 (28.9)	95 (36.1)	92 (38.0)
S. anginosus Group	30 (19.9)	21 (16.4)	27 (24.1)	28 (24.6)	57 (21.7)	49 (20.2)
S. pyogenes	12 (7.9)	11 (8.6)	5 (4.5)	4 (3.5)	17 (6.5)	15 (6.2)
S. mitis Group	5 (3.3)	3 (2.3)	9 (8.0)	3 (2.6)	14 (5.3)	6 (2.5)

Table 3. Treatment-emergent safety profile in patients with wound infections.

Safety Parameter, n (%)	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 (<1)	0	0	0	1 (<1)
Serious AEs	3 (2)	7 (5)	3 (2)	3 (2)	6 (2)	10 (3)
AEs leading to discontinuation	4 (2)	9 (6)	3 (2)	5 (4)	7 (2)	14 (5)
Any AE	114 (63)	85 (54)	53 (42)	61 (46)	167 (54)	146 (50)
Drug-related AEs	49 (27)	39(25)	16 (13)	17(13)	65 (21)	56 (19)
Most common AEs (>5%)						
Nausea	23 (13)	14 (9)	9 (7)	9 (7)	32 (10)	23 (8)
Headache	29 (16)	19 (12)	4 (3)	7 (5)	33 (11)	26 (9)
Vomiting	12 (7)	11 (7)	3 (2)	5 (4)	15 (5)	16 (6)
Diarrhea	4 (2)	11 (7)	2 (2)	6 (5)	6 (2)	17 (6)
Infusion site extravasation	11 (6)	9 (6)	10 (8)	7 (5)	21 (7)	16 (6)
Fatigue	17 (9)	7 (5)	0	1 (1)	17 (6)	8 (3)
Secondary skin bacterial infection	14 (8)	9 (6)	2 (2)	1 (1)	16 (5)	10 (3)

Figure 1.

Disposition of patients in the pooled REVIVE-1 and REVIVE-2 studies.

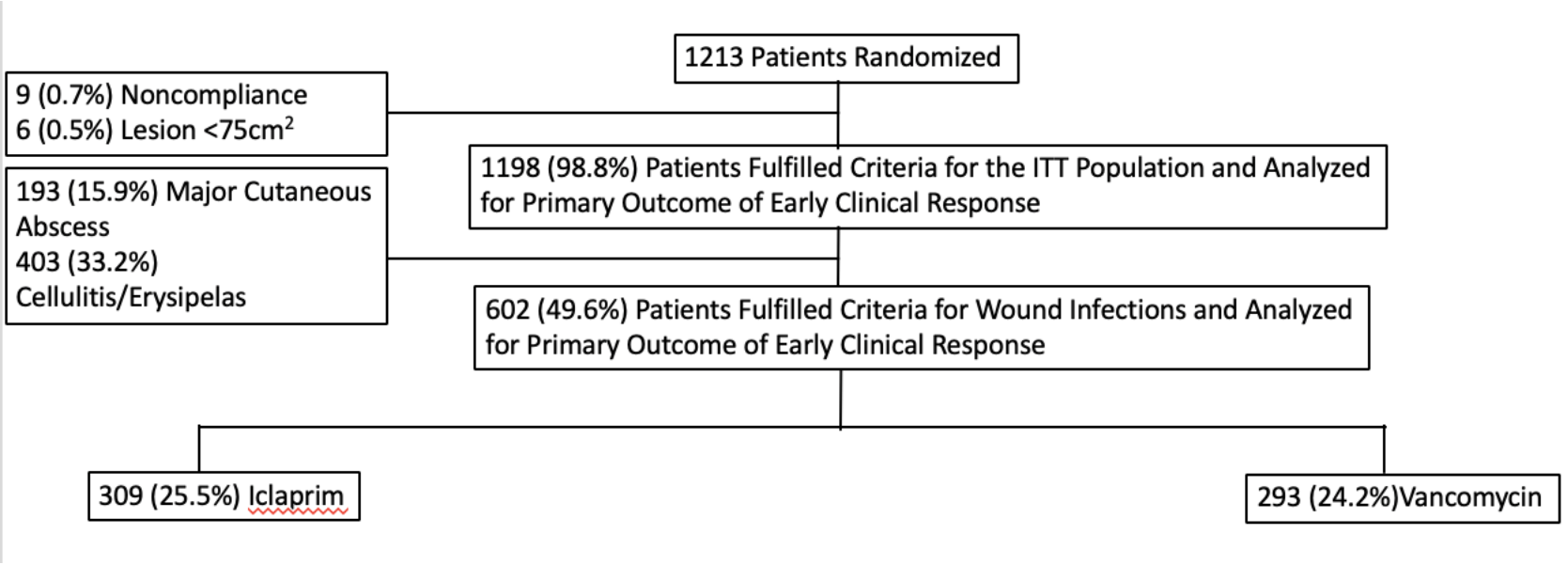

Figure 2.

Early clinical response at the early time point for iclaprim and vancomycin arms in patients with wound infections in the REVIVE studies.