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Huang, DB, Corey, GR, Holland, TL et al. (8 more authors) (2018) 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. International Journal of Antimicrobial Agents, 52 (2). pp. 233-240. ISSN 0924-8579

https://doi.org/10.1016/j.ijantimicag.2018.05.012

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

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ABSTRACT

Iclaprim, a diaminopyrimidine antimicrobial, was compared with vancomycin for treatment of patients with acute bacterial skin and skin-structure infections (ABSSSIs) in two studies (REVIVE-1 and REVIVE-2). Here, the efficacy and tolerability of iclaprim in a pooled analysis of results from both studies was explored. REVIVE-1 and REVIVE-2 were phase 3, double-blind, randomised, multicentre, active-controlled, non-inferiority (margin of 10%) trials, each designed to enrol 600 patients with ABSSSI using identical study protocols. Iclaprim 80 mg and vancomycin 15 mg/kg were administered intravenously every 12 h for 5–14 days. The primary endpoint was a ≥20% reduction from baseline in lesion size [early clinical response (ECR)] at the early time point (ETP) (48–72 h after starting study drug) in the intent-to-treat population. In REVIVE-1, ECR at the ETP was 80.9% with iclaprim versus 81.0% with vancomycin (treatment difference −0.13%, 95% CI −6.42% to 6.17%). In REVIVE-2, ECR was 78.3% with iclaprim versus 76.7% with vancomycin (treatment difference 1.58%, 95% CI –5.10% to 8.26%). The pooled ECR was 79.6% with iclaprim versus 78.8% with vancomycin (treatment difference 0.75%, 95% CI –3.84 to 5.35%). Iclaprim and vancomycin were comparable for the incidence of mostly mild adverse events, except for a higher incidence of elevated serum creatinine with vancomycin (n = 7) compared with iclaprim (n = 0). Iclaprim achieved non-inferiority compared with vancomycin for ECR at the ETP and secondary endpoints with a similar safety profile in two phase 3 studies for treatment of ABSSSI suspected or confirmed as caused by Gram-positive pathogens. [Clinical Trials Registration. NCT02600611 and NCT02607618.]

1. Introduction

Up to 1.8% of all hospitalisations are due to acute bacterial skin and skin-structure infections (ABSSSIs) [1]. Often these serious skin infections require intravenous (i.v.)

antimicrobials, hospitalisation and/or surgical intervention [2,3]. The majority of ABSSSIs are caused by Gram-positive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), methicillin-susceptible S. aureus and β-haemolytic streptococci [3,4]. Although many antimicrobials are available to treat ABSSSIs, only a few are available for ABSSSI caused by multidrug-resistant bacteria, and some of these are limited by safety, tolerability and dosing issues [5], the need for monitoring plasma concentrations and/or inconvenient dosage regimens [6]. Alternative antimicrobials are needed for ABSSSIs that provide improved efficacy and safety in infections caused by multidrug-resistant bacteria [6,7].

Iclaprim is a selective inhibitor of bacterial dihydrofolate reductase, the same mechanism of action as trimethoprim (TMP). However, iclaprim is more potent than TMP (i.e. lower MIC90, greater binding affinity to bacteria, better pharmacokinetics/pharmacodynamics) [6]. Iclaprim is rapidly bactericidal and is active against a range of Gram-positive pathogens, including those that are resistant to TMP and other antimicrobials, including vancomycin, linezolid and daptomycin [8–11]. Unlike trimethoprim/sulfamethoxazole, iclaprim does not need to be combined with a sulfonamide, which are associated with hypersensitivity and/or allergic reactions. Iclaprim has also been shown to supress bacterial toxin production, which may be important in necrotizing skin infections [12]. In two phase 3 studies of patients treated for ABSSSI (REVIVE-1 and REVIVE-2), iclaprim was non-inferior to vancomycin for early clinical response (ECR) at the early time point (ETP) in the intent-to-treat (ITT) population. Here, a pooled analysis was conducted of the two phase 3 REVIVE studies to further evaluate the safety and efficacy of iclaprim for patients with ABSSSI due to Gram-positive pathogens.

2. Materials and methods

2.1. Study design

Both REVIVE-1 and REVIVE-2 were phase 3, double-blind, randomised (1:1), multicentre, active-controlled, non-inferiority studies that utilised identical study protocols (NCT02600611 and NCT02607618, respectively). 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 REVIVE1 [13] and between January 2016 and August 2017 for REVIVE-2 [14]. Study protocols and informed consent forms were reviewed and approved by an institutional review board at each study site, and all patients or their authorised representative provided written informed consent prior to any study-specific procedures.

2.2. Patient selection

Eligible patients included males and females aged ≥18 years with suspected or confirmed ABSSSI due to Gram-positive pathogens. ABSSSI was defined as a bacterial skin infection with a lesion size ≥75 cm2 and included major cutaneous abscess, cellulitis/erysipelas and/or wound infections caused by external trauma (e.g. needle sticks or insect bites). Patients enrolled had purulent or seropurulent drainage before or after surgical intervention of a wound or at least three signs and symptoms from among the following: discharge; erythema (extending ≥2 cm beyond

a wound edge in one direction); swelling and/or induration; heat and/or localised warmth; and/or pain and/or tenderness to palpation. Detailed inclusion/exclusion criteria are provided elsewhere [13,14].

2.3. Study treatments

Patients were randomised 1:1 to either iclaprim or vancomycin. Iclaprim was administered as a fixed dose of 80 mg (patients with no hepatic impairment or Child–Pugh Class A) or 40 mg (Child–Pugh Class B) intravenously every 12 h (q12h). Child–Pugh C patients were excluded. Vancomycin was administered at 15 mg/kg intravenously. The vancomycin dose was q12h for creatinine clearance (CLCr) ≥50 mL/min, every 24 h for CLCr of 35–49 mL/min or every 48 h for CLCr of 25–34 mL/min, or was based on vancomycin trough levels. A pharmacist unblinded to treatment assignment prepared i.v. infusions for patients who were assigned to vancomycin and maintained the same infusion regimen as used for iclaprim. For each patient, the pharmacist used the CLCr or vancomycin trough level (to which the investigator was blinded) to adjust the vancomycin dosage to maintain a trough level of 10–15 mg/L for patients with a micro-organism with a minimum inhibitory concentration (MIC) of ≤1 mg/L or a trough level of 15–20 mg/L for those with MIC > 1 mg/L. Iclaprim and vancomycin doses were added to 500 mL of normal saline and were infused intravenously over 120 min. Blinding was maintained when vancomycin was dosed at an interval longer than q12h by using normal saline (placebo) infusions. The first dose of study medication was received within 24 h of randomisation, and study drugs were administered for a minimum of 5 days and up to 14 days based on assessment of resolution of signs and symptoms of ABSSSI by the study investigator at each site.

Concomitant antimicrobial treatment with aztreonam or metronidazole was permitted for patients where a Gram-negative or anaerobic pathogen was identified from Gram stain or specimen culture. Other systemic antimicrobials or topical antimicrobials at the site of the ABSSSI were prohibited.

2.4. Study assessments

Prior to randomisation, specimens from purulent discharge from a wound or abscess as well as aspirate or skin biopsy from the leading edge of cellulitis were obtained from patients for microbiological evaluation, and additional specimens were obtained at subsequent visits for patients with persistent clinical signs or symptoms. Microbiological specimens were evaluated by a local microbiology laboratory, and isolates were subcultured and sent to a central microbiology laboratory for confirmation of bacteria and for determination of MICs. Investigators were encouraged to obtain leading-edge punch biopsies for patients with cellulitis. Serological tests [antistreptolysin O (ASO) titres] were obtained for all patients. Blood samples for aerobic/anaerobic culture were obtained 10 min apart from different peripheral sites within 24 h of the first dose of study drug.

2.5. Study endpoints

The primary efficacy endpoint was the proportion of patients who achieved an ECR (≥20% reduction in lesion size compared with baseline) at the ETP, which was 48–72 h after starting the study drug, in the ITT population. Secondary endpoints included clinical cure rate at the test of cure (TOC) (7–14 days after the last dose of study drug), measured both by traditional assessment and by a modified composite TOC assessment in the ITT population, as well as the safety and tolerability of iclaprim and vancomycin. Clinical cure at the TOC visit was evaluated using two pre-specified definitions: (i) complete resolution of all signs and symptoms of ABSSSI with no further antimicrobial treatment (except aztreonam or metronidazole for polymicrobial infections) or surgical procedure; and (ii) a modified clinical cure at TOC that required a ≥90% reduction from baseline in lesion size, no increase in lesion size since the ETP, and no additional antimicrobials or unplanned significant surgical procedures after the ETP. The modified clinical cure allowed for an objective measure (i.e. 90% reduction in lesion size) similar to the ECR (≥20% reduction in lesion size). Patients were evaluated at baseline, daily through the ETP, and every 48–72 h through end of therapy (EOT). The TOC assessment was conducted 7–14 days post-EOT, followed by a late follow-up phone call conducted 28–32 days after the first dose (Fig. 1).

Fig. 1. Study design for phase 3, double-blind, randomised (1:1), multicentre, active-controlled, global non-inferiority studies of iclaprim versus vancomycin in patients with acute bacterial skin and skin-structure infections (ABSSSIs) at 71 trials sites in Europe, Latin American and the USA from REVIVE-1 and REVIVE-2. IV, intravenous; q12h, every 12 h.

Safety was assessed based on treatment-emergent adverse events (AEs), clinical laboratory tests (clinical chemistry, coagulation, haematology, liver function tests), urinalysis, vital signs, physical examinations and electrocardiograms (ECGs).

2.6. Statistical analysis

Comparisons of efficacy outcomes between treatment groups were based on non-inferiority as a one-sided hypothesis test performed at the 2.5% level of significance and was based on the lower limit of the two-sided 95% confidence interval (CI). The non-inferiority bound was 10% in each of the original trials based on the FDA guidance [15]. If the lower bound of the two-sided 95% CI based on the Z-test with unpooled variance estimate was greater than –0.100, then non-inferiority of iclaprim to vancomycin was to be declared. Continuous data were summarised by treatment group using the number of patients in the analysis population, mean ± standard deviation and median (range), and categorical data were summarised by treatment group using number and percentage. Demographics and baseline characteristics were summarised using descriptive statistics. The primary efficacy analysis and secondary analyses in predefined populations were performed in the ITT population. For patients with a confirmed Gram-positive pathogen at baseline, bacteriological outcomes at EOT and TOC were presented as frequency distributions by treatment group. The safety population included all randomised patients who received at least one dose of study medication. The sample size for each study was estimated using the Farrington and Manning method for non-inferiority testing with a one-sided α of

0.025. Assuming a 75% ECR rate at the ETP in each group and a 10% non-inferiority bound δ, a sample size of 295 patients both in the iclaprim and vancomycin groups was required for 80% power in each study. A minimum of 600 patients (ca. 300 per treatment group) was to be randomised (1:1) in the ITT population in each study.

Pooling of the data across the studies allowed for review of the data across a larger sample size, which is particularly relevant for potentially serious AEs (i.e. elevations in transaminases and QTc interval) and for specific secondary endpoints with lower sample size (e.g. by pathogen responses) than the individual studies.

3. Results

3.1. Baseline demographics and clinical characteristics

In total, 1198 patients were randomised and met the criteria for the ITT population (Fig. 2). Demographic, clinical characteristics at baseline and type of skin infection generally were comparable between the iclaprim and vancomycin groups and between studies (Table 1). More patients had wound infections (56.9% vs. 43.7%) and fewer patients had cellulitis/erysipelas (27.3% vs. 40.0%) in both treatment groups in REVIVE-1 compared with REVIVE-2. In both REVIVE-1 and REVIVE-2, a large number of patients in the iclaprim group reported illicit i.v. drug use (63.4% and 46.4%, respectively). For both REVIVE-1 and REVIVE-2, the median treatment duration was 7 days both for iclaprim and vancomycin.

3.2. Efficacy

3.2.1. Primary efficacy endpoint

In REVIVE-1, an ECR was reported at the ETP for 80.9% of patients treated with iclaprim and 81.0% of patients treated with vancomycin (treatment difference −0.13%, 95% CI −6.42% to 6.17%) (Fig. 3). In REVIVE-2, an ECR was reported at the ETP for 78.3% of patients treated with iclaprim and 76.7% of patients treated with vancomycin (treatment difference 1.58%, 95% CI –5.10% to 8.26%). For the pooled REVIVE-1 and REVIVE-2, ECR was reported at the ETP for 79.6% of patients with iclaprim and 78.8% of patients with vancomycin (treatment difference 0.75%, 95% CI –3.84% to 5.35%).

3.2.2. Secondary outcomes

In REVIVE-1, the clinical cure rates at TOC were 83.2% and 87.3% of patients in the iclaprim and vancomycin groups, respectively (treatment difference −4.11%, 95% CI −9.78% to 1.56%). Using a modified clinical cure TOC analysis, clinical cure was observed in 76.2% and 80.0% of patients treated with iclaprim and vancomycin, respectively (treatment difference −3.83%, 95% CI −10.45% to 2.80%).

In REVIVE-2, the clinical cure rates at TOC were 77.6% and 77.7% for patients in the iclaprim and vancomycin groups, respectively (treatment difference –0.08%, 95% CI –6.74% to 6.59%). Using a modified clinical cure TOC analysis, clinical cure was observed in 71.5% and 70.5% of patients in the iclaprim and vancomycin groups,

respectively (treatment difference 1.03%, 95% CI –6.23% to 8.29%).

Fig. 2. Disposition of patients in the pooled REVIVE-1 and REVIVE-2 studies. ITT, intent-to treat.

Table 1
Baseline and demographic characteristics in the intent-to-treat population, by treatment, from REVIVE-1 and REVIVE-2 and pooled REVIVE-1 and REVIVE-2.

Fig. 3. Early clinical response (ECR) at the early time point for iclaprim and vancomycin from REVIVE-1 and REVIVE-2 and pooled REVIVE-1 and REVIVE-2. CI, confidence interval

Fig. 4. Forest plot for analysis of the difference in early clinical response (ECR) rates at the early time point (ETP) by subgroup, and clinical response rates in the intent-totreat (ITT) population from pooled REVIVE-1 and REVIVE-2. MRSA, methicillin-resistant Staphylococcus aureus (MRSA);MSSA, methicillin-susceptible S. aureus; TOC, test-ofcure; CI, confidence interval.

In the pooled REVIVE-1 and REVIVE-2, the clinical cure rates at TOC were 80.4% and 82.5% for patients in the iclaprim and vancomycin groups, respectively (treatment difference –2.04%, 95% CI –6.44% to 2.36%) (Fig. 4). Using a modified clinical cure at TOC analysis, clinical cure was observed in 73.9% and 75.2% of patients in the iclaprim and vancomycin groups, respectively (treatment difference –1.34%, 95% CI –6.28% to 3.59%). The ECR at the ETP was comparable for iclaprim and vancomycin among subgroups predefined by lesion type, pathogen (see below), diabetes and renal impairment (Fig. 4); however, the studies were not powered to examine efficacy differences according to such subgroups.

For the pooled Streptococcus pyogenes, confirmed by culture from the ABSSSI, the ECR was higher at the ETP among patients receiving iclaprim compared with vancomycin [22/24 (91.7%) vs. 20/28 (71.4%), respectively]; however, the clinical cure rate was lower at the TOC among patients receiving iclaprim compared with vancomycin [12/24 (50.0%) vs. 20/28 (71.4%), respectively]. The lower clinical cure rate at TOC among patients receiving iclaprim compared with vancomycin was driven by an increased loss to follow-up and an increased number of i.v. drug abusers (11 for iclaprim and 7 for vancomycin). For S. pyogenes, confirmed by positive culture or positive ASO titres, the ECR was similar at the ETP among patients receiving iclaprim, reported in 180 (76.9%) of 234 patients, and in those receiving vancomycin, reported in 184 (76.0%) of 242 patients; the clinical cure rate was also similar at TOC among patients receiving iclaprim, reported in 182 (77.8%) of 234 patients, and in those receiving vancomycin, reported in 198 (81.8%) of 242 patients.

Table 2
Microbiological findings at baseline in the intent-to-treat population, by treatment, from REVIVE-1 and REVIVE-2 and pooled REVIVE-1 and REVIVE-2.

In the pooled REVIVE-1 and REVIVE-2, 455 (76.1%) of the 598 ITT patients had a culture-confirmed Gram-positive pathogen identified at baseline in REVIVE-1 as did

386 (64.3%) of 600 ITT patients in REVIVE-2 (Table 2). Staphylococcus aureus was the most commonly isolated pathogen (n = 595), of which 45.9% were MRSA. Both in REVIVE-1 and REVIVE-2, the MIC50/MIC90 values for iclaprim and vancomycin for S. aureus isolates were 0.12/0.5 μg/mL and 1/1 μg/mL, respectively. Streptococcus pyogenes was uncommonly isolated (n = 52). The MIC50/MIC90 values for iclaprim and vancomycin for S. pyogenes isolates were 0.12/0.5 μg/mL and 0.12/0.5 μg/mL, respectively.

3.2.3. Other outcomes

In a comparison between iclaprim and vancomycin for patients with vancomycin dose modulation, 472 (79.6%) of 593, 6 (75.0%) of 8, and 471 (78.9%) of 597 patients randomised to iclaprim, vancomycin that required dose modulation, and vancomycin that did not require dose modulation, respectively, had an ECR at ETP. In a comparison between iclaprim and vancomycin based on pathogen MIC, 228 (85.4%) of 267, 13 (76.5%) of 17, 1 (100%) of 1, and 10 (62.5%) of 16 patients randomised to iclaprim had an ECR to S. aureus with iclaprim MICs of ≤0.25, 0.5–1, >1–4, and ≥8 μg/mL. For patients randomised to vancomycin, 0, 242 (82.6%) of 293, 1 (100%) of 1, and 0 patients had an ECR to S. aureus with vancomycin MICs of ≤0.25, 0.5–1, >1–4, and ≥8 μg/mL.

3.3. Safety and tolerability

The incidence of treatment-emergent AEs for REVIVE-1 and REVIVE-2 among patients included in the safety population in the iclaprim and vancomycin treatment groups are shown in Table 3. In REVIVE-1 and REVIVE-2, the incidence of AEs leading to study drug discontinuation and serious AEs were similar for patients in the iclaprim and vancomycin groups. Across REVIVE-1 and REVIVE2, there were no deaths reported in patients who received iclaprim compared with 3 deaths (0.5%) in patients who received vancomycin.

No significant differences were observed between iclaprim or vancomycin groups in mean values or mean changes in routine serum laboratory parameters (except serum creatinine), urinalysis, vital signs or physical examinations during drug treatment. No patient in either study met Hy's law criteria.

No drug-related AEs related to nephrotoxicity were reported with iclaprim, and seven (1.2%) severe AEs related to nephrotoxicity or shifts in serum creatinine to >3 × upper limit of normal (ULN) were reported with vancomycin.

Both in REVIVE-1 and REVIVE-2, one patient (0.2%) in each study in the iclaprim group had a corrected QTcF interval >500 ms (559 ms with a pre-dose value of 527 ms in REVIVE-1 and 503 ms in REVIVE-2). Both patients with QTcF prolongation resolved to baseline values after the end of the iclaprim infusion that the patient received when the ECG was obtained.

4. Discussion

This was a pooled analysis of fixed-dose iclaprim compared with vancomycin for patients with ABSSSI. In contrast to weightbased dosing employed in earlier

complicated skin and skinstructure infection clinical trials, the REVIVE-1 and REVIVE-2 ABSSSI studies used a fixed dose of iclaprim at 80 mg q12h. The fixed dose was selected because, compared with the weight-based dosing regimen, the fixed-dose regimen increased both the area under the concentration–time curve/MIC ratio (AUC/MIC) by ca. 28% and the time above the MIC (T>MIC) by ca. 32% [16]. These two parameters (AUC/MIC and T>MIC) were identified as closely associated with efficacy in animal infection models [17]. In addition, the fixed-dose regimen reduces the maximum concentration at steadystate (Cmax,ss) by ca. 9%, which was associated with QTc prolongation in phase 1 studies.

In the pooled analyses, iclaprim and vancomycin were comparable for the prespecified primary endpoint of ECR at ETP and for secondary endpoints including clinical cure rates and among subgroups identified by co-morbidity, type of infection, pathogen and AEs in the treatment of patients with ABSSSI that was suspected or confirmed to be due to Gram-positive organisms. No unexpected safety issues were identified with iclaprim. In the pooled analyses, patients receiving vancomycin experienced increases in serumcreatinine from baseline despite dose adjustment based on CLCr or vancomycin trough levels, and seven vancomycin recipients had AEs related to nephrotoxicity. In contrast, there were no reported AEs related to nephrotoxicity in patients treated with iclaprim, and the changes from baseline in serum creatinine were minimal.

Table 3
Incidence of adverse events (AE) in the safety population, by treatment, from REVIVE-1 and REVIVE-2 and pooled REVIVE-1 and REVIVE-2 occurring in ≥2% of patients in either pooled treatment group.

Because iclaprim was not nephrotoxic in this pooled analysis, it could be considered for treatment of ABSSSI among patients with or at risk of renal impairment. Also, because of its different mechanism of action, iclaprim could be considered for use in the treatment of ABSSSI in patients with pathogens that are resistant or non-susceptible to standard-of-care antimicrobials, including vancomycin, daptomycin and/or linezolid [11].

The individual studies and the pooled analysis have limitations and the results may not be generalisable to other practice settings. First, 68.8% of patients in REVIVE-1 and REVIVE-2 were from the USA, 29.0% from Europe and 2.2% from Latin America, thus the results may not be generalisable to other locations [13,14]. Second, vancomycin trough concentrations were not available. The vancomycin consensus guidelines do not recommend a specific target trough concentration range for adult patients with ABSSSI. However, based on adherence to the prespecified vancomycin dosing nomogram, >95% of patients had the correct dosing interval for this antimicrobial, including those patients with renal impairment (CLCr < 75 mL/min) for whom the initial dosing interval was based on renal clearance. Third, in the pooled REVIVE analyses, there was only one S. aureus with a vancomycin MIC > 1 mg/L identified from patients randomised to vancomycin. Fourth, because of the challenges faced when collecting microbiological samples in patients with cellulitis, only 52 patients had cultures positive for S. pyogenes in the pooled REVIVE analysis. Although the study protocols included measures to enrich the

study population for S. pyogenes using leading-edge punch biopsies and serological tests, only 4.3% of patients had this pathogen detected. Last, an imbalance was observed in the number of patients lost to follow-up between iclaprim and vancomycin in REVIVE-1 (but not REVIVE-2), largely driven by a greater number of i.v. drug users in the iclaprim arm. As these patients are treated as failures, this imbalance may underestimate the efficacy of iclaprim relative to vancomycin.

In conclusion, the pooled results from two phase 3 studies in patients with ABSSSI caused by Gram-positive micro-organisms confirm that iclaprim was non-inferior to vancomycin for ECR at the ETP, secondary endpoints and safety. Thus, iclaprim provides an option for treating ABSSSIs caused by Gram-positive pathogens, including infections caused by antimicrobial-resistant bacteria. In patients hospitalised with ABSSSI and with co-morbidities includingdiabetes or renal impairment, the fixed-dose regimen, no requirement for therapeutic drug monitoring and lack of nephrotoxicity with iclaprim may offer benefits over vancomycin.

Acknowledgments

Editorial assistance was provided by Richard Perry, PharmD, and was supported by Motif BioSciences (New York, NY).

Funding

This work was supported by Motif Bio plc (New York, NY).

Competing interests

DBH is an employee of Motif BioSciences; TLH has received consultancy fees from Basilea Pharmaceutica, Genentech, The Medicines Company and Motif Biosciences, and grant support from Basilea and Achaogen; TMF has served as a consultant for Motif BioSciences, GSK, Meiji, Merck, Nabriva, Paratek, Cempra and Shionogi; AT has served as a consultant for Motif BioSciences; MHW has received consulting fees from Abbott Laboratories, Actelion, Astellas, AstraZeneca, Bayer, bioMérieux, Cerexa, Cubist, Durata, The European Tissue Symposium, The Medicines Company, MedImmune, Merck, Motif Biosciences, Nabriva, Optimer, Paratek, Pfizer, Qiagen, Roche, Sanofi-Pasteur, Seres, Summit and Synthetic Biologics, lecture fees from Abbott, Alere, Astellas, AstraZeneca, Merck, Pfizer and Roche, and grant support from Abbott, Actelion, Astellas, bioMérieux, Cubist, Da Volterra, MicroPharm, Morphochem A G, Sanofi-Pasteur, Seres, Summit, The European Tissue Symposium and Merck; MD has received speaker's and/or consultancy fees from AstraZeneca, Bayer, Janssen-Cilag, Motif BioSciences, Novartis, Pfizer and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.; GRC has received consultancy fees from Cempra Pharmaceuticals, PRA International, Furiex Pharmaceuticals, Inimex Pharmaceuticals, Dr Reddy's Laboratories, Cubist Pharmaceuticals, Cerexa/Forest Laboratories, AstraZeneca, GlaxoSmithKline, Pfizer, Merck, Trius Therapeutics, ContraFect, Theravance and Astellas Pharma, has served on advisory boards for Pfizer, PolyMedix, Trius Therapeutics, Rib-X Pharmaceuticals, Seachaid Pharmaceuticals, BioCryst Pharmaceuticals, Durata Therapeutics, Achaogen, Gilead Sciences, ContraFect, Cempra and Nabriva Therapeutics, and has received research grants from Theravance, Innocoll and The

Medicines Company; and BB and ED work for Veristat, LLC, which is a contract research organisation that has received consulting fees from Motif. All other authors declare no competing interests.

Ethical approval

Study protocols and informed consent forms were reviewed and approved by an institutional review board at each study site, and all patients or their authorised representative provided written informed consent prior to any study-specific procedures.

References

[1] Kaye KS, Patel DA, Stephens JM, Khachatryn A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. PLoS One 2015;10:e0143276.
[2] Magill SS, Edwards JR, Bamberg W, Bedavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198–208.
[3] Moran GJ, Abrahamian FM, Lovecchio F, Talan DA. Acute bacterial skin infections: developments since the 2005 Infectious Diseases Society of America (IDSA) guidelines. J Emerg Med 2013;44:e397–412.
[4] Jenkins TC, Knepper BC, Jason Moore S, Saveli CC, Pawlowski SW, Perlman DM, et al. Microbiology and initial antibiotic therapy for injection drug users and non-injection drug users with cutaneous abscesses in the era of community-associated methicillin-resistant Staphylococcus aureus. Acad Emerg Med 2015;22:993–7.
[5] Nannini E, Murray BE, Arias CA. Resistance or decreased susceptibility to glycopeptides, daptomycin, and linezolid in methicillin-resistant Staphylococcus aureus. Curr Opin Pharmacol 2010;10:516–21.
[6] Bassetti M, Righi E, Carnelutti A. New therapeutic options for skin and soft tissue infections. Curr Opin Infect Dis 2016;29:99–108.
[7] Edelsberg J, Berger A, Weber DJ, Mallick R, Kuznick A, Oster G. Clinical and economic consequences of failure of initial antibiotic therapy for hospitalized patients with complicated skin and skin-structure infections. Infect Control Hosp Epidemiol 2008;29:160–9.
[8] Sader HS, Fritsche TR, Jones RN. Potency and bactericidal activity of iclaprim against recent clinical Gram-positive isolates. Antimicrob Agents Chemother 2009;53:2171–5.
[9] Schneider P, Hawser S, Islam K. Iclaprim, a novel diaminopyrimidine with potent activity on trimethoprim sensitive and resistant bacteria. Bioorg Med Chem Lett 2003;13:4217–21.
[10] Huang DB, Jr File TM, Dryden M, Corey GR, Torres A, Wilcox MH. Surveillance of iclaprim activity: in vitro susceptibility of Gram-positive pathogens collected from 2012 to 2014 from the United States, Asia Pacific, Latin America and Europe. Diagn Microbiol Infect Dis 2018;90:329–34.
[11] DB Huang, Hawser S, Gemmell CG, Sahm DF. In vitro activity of iclaprim against methicillin-resistant Staphylococcus aureus nonsusceptible to daptomycin, linezolid, or vancomycin: a pilot study. Can J Infect Dis Med Microbiol 2017:3948626.

[12] Bryant AE, Katahira E, Huang DB, Stevens DL. Effects of iclaprim and trimethoprim on exotoxin production by methicillin-resistant Staphylococcus aureus. IDWeek, San Diego: Infectious Diseases Society of America; 2017. October 4–8.
[13] Huang DB, O'Riordan W, Overcash JS, Heller B, Amin F, File TM, et al. A phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim vs 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;66:1222–9.
[14] Holland TL, O'Rioridan WO, McManus A, Shin E, Borgehei A, File TM, 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-2. Antimicrob Agents Chemther 2018;62 e02580-17.
[15] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research.. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment, Silver Spring, Maryland: CDER; 2013. October.
[16] Lodise TP, Bosso J, Kelly C, Williams PJ, Lane JR, Huang DB. Pharmacokinetic and pharmacodynamic analyses to determine the optimal fixed dosing regimen of iclaprim for treatment of patients with serious infections caused by Gram-positive pathogens. Antimicrob Agents Chemother 2018;62 e01184-17.
[17] Park JH, Craig W, Marchillo K, Huang DB, Andes DR. Identification of the in vivo pharmacokinetics and pharmacodynamic driver of iclaprim. Antimicrob Agents Chemother 2018;62 e02550-17