

Present and Emerging Therapies for Methicillin-Resistant *Staphylococcus aureus* Skin and Soft Tissue Infections: Focus on Iclaprim

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Abstract: The management of skin and soft-tissue infections caused by multidrug resistant Gram-positive organisms, specifically methicillin-resistant *Staphylococcus aureus* (MRSA), continues to be a significant challenge for clinicians. Iclaprim is a diaminopyrimidine that has shown potent activity against various Gram-positive organisms, including MRSA, with limited Gram-negative activity similar to that of trimethoprim. Iclaprim has completed two Phase III trials with a submission of New Drug Application to the United States Food and Drug Administration (FDA) in 2008. Subsequently, a complete response letter not supporting the approval of iclaprim was released by the FDA. More recently, Acino Holding Ltd. has acquired the shares and data to iclaprim. Pending final draft guidance from the FDA for future studies, iclaprim may have a role in the management of skin and soft-tissue infections. A Medline search of articles through February 2011 and references of selected citations was conducted. Data from abstracts presented at the International Conference on Antimicrobial Agents and Chemotherapy and the Infectious Diseases Society of America annual meetings were also appraised. This article reviews the antimicrobial profile, pharmacokinetic and pharmacodynamic properties, and available clinical data of iclaprim.

Keywords: Gram-positive, antimicrobials, iclaprim, skin and soft tissue, MRSA

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Introduction

Skin and soft-tissue infections (SSTIs) encompass a wide spectrum of infections from superficial impetigo and mild cellulitis to severe infections involving deeper fascia (eg, necrotizing fasciitis and surgical-site infections) depending on the anatomical site of infection and the associated organisms involved¹ (Table 1).

Although SSTIs are commonplace in the community as well as nosocomial settings, recent changes in the epidemiology of causative organisms have resulted in substantial changes in the management of SSTIs.²⁻⁶ More specifically, the frequent isolation of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) as a causative organism in cellulitis, abscesses, and necrotizing fasciitis has underscored the importance of empiric coverage for methicillin-resistant *Staphylococcus aureus* (MRSA).

S. aureus has shown a remarkable ability to evolve alongside antimicrobial advancement.² In just a few years after mass production of the first antibiotic, penicillin, a *S. aureus* isolate demonstrating resistance via the production of penicillinase was isolated in 1947. Because the gene encoding penicillinase was plasmid-mediated, the production of penicillinase quickly spread throughout most clini-

cal isolates of *S. aureus*, as well as other species of staphylococci. The introduction of methicillin with a bulky side group in 1959 circumvented the problem of penicillinase-producing *S. aureus*. However, the survival of *S. aureus* was renewed for many decades with the acquisition of *mecA* gene, which altered the binding site of anti-staphylococcal penicillins.³

Over the past two decades, the prevalence of *S. aureus* strains resistant to methicillin has steadily increased.^{4,5} More specifically, data from the Surveillance Network-USA reported MRSA rates of 59.2%, 55%, and 47.9% for strains from non-intensive care unit (ICU) patients, ICU patients, and outpatients, respectively.⁵ The remarkable spread of MRSA as a cause of community-acquired infections may have contributed to its increasing prevalence, characterized by reports of a number of infections and associated syndromes involving skin and soft-tissue such as cellulitis, abscesses, necrotizing skin infections, necrotizing fasciitis, pyomyositis, septic thrombophlebitis of the extremities, and pelvic syndrome.⁶⁻¹⁰

Meanwhile, several controversies have surfaced recently, regarding the therapeutic betterment of treating skin abscesses with adjunctive antimicrobial therapy in addition to incision and drainage,^{11,12} and the selection of antimicrobial agents for various clinical presentations of SSTIs. More specifically, in 66 and 103 patients admitted for the management of cellulitis and cutaneous abscess, respectively, broad-spectrum antimicrobial agents with activity against Gram-negative bacilli was initiated in 61% and 67% of the patients in each respective classification.¹³ In this study, a Gram-positive organism (mostly MRSA) was the predominant organism isolated from patients with cellulitis and cutaneous abscesses without complicating factors (deep tissue infection, bacteremia, intensive care admission, diabetic ulcer, peripheral arterial disease, recurrent cellulitis, human or animal bite, severe cellulitis necessitating surgical debridement or fascial biopsy, necrotizing fasciitis, periorbital or perirectal involvement). It should be noted that in 77 positive cultures identified for cutaneous abscesses, a Gram-negative pathogen was isolated in only 13% of the cases,¹³ which is consistent with what was previously reported for intact-skin SSTIs.^{1,13}

Iclaprim is a newer generation of the diaminopyrimidines with the potential to meet the challenges of managing skin and soft tissue infections. It selectively

Table 1. Common pathogens in selected skin and soft-tissue infections.

Type of Infection	Pathogens
Impetigo, erysipelas, cellulitis	<i>Staphylococcus aureus</i> group A streptococci
Furuncles, carbuncles, abscesses	<i>Staphylococcus aureus</i>
Necrotizing skin infections	group A streptococci <i>Staphylococcus aureus</i> <i>Clostridium</i> spp. Polymicrobial (post-operative)
Animal/human bites	<i>Staphylococcus aureus</i> <i>Fusobacterium</i> spp. <i>Pasteurella multocida</i> <i>Eikenella corrodens</i>
Surgical wound infections	<i>Staphylococcus aureus</i> group A streptococci ± enterobacteriaceae, anaerobes
Catheter-associated infections	<i>Staphylococcus aureus</i> coagulase-negative staphylococci



inhibits the dihydrofolate reductase (DHFR) enzyme, similar to the actions of trimethoprim (TMP). Since the discovery of TMP in 1965, major pharmaceutical companies have conducted test phases using mutations from the DHFR gene to understand the mechanism of TMP-resistance in order to design a new DHFR inhibitor that is active against multidrug-resistant *S. aureus*.¹⁴ Iclaprim was initially developed by Roche and subsequently acquired by Arpida Ltd. An intravenous formulation of iclaprim has completed two phase 3 studies in complicated skin and skin structure infections (cSSSI) caused by Gram-positive organisms, followed by submission of New Drug Application to the United States (US) Food and Drug Administration (FDA) in 2008. After a recommendation from the advisory committee in 2008, the US FDA issued a complete response letter not supporting the approval of iclaprim for use in cSSSI in 2009.¹⁵ This article briefly summarizes current US FDA approved intravenous Gram-positive agents for the management of SSTIs, and focuses on the potential role of iclaprim in the management of SSTIs.

A systematic literature review of PubMed was conducted from inception to February 2011 using the following combination of key words: skin, soft tissue, iclaprim, AR-100 and RO-48-2622 (2002–2010). Additional sources included the manufacturer website, www.clinicaltrials.gov and FDA. Due to the paucity of data, abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy as well as the Infectious Diseases Society of America (IDSA) were also included.

Current Approved Gram-positive Agents

The rapid spread of CA-MRSA has led to dramatic increases in healthcare visits, particularly in the ambulatory care and emergency department settings.^{6–10,16–18} Although trimethoprim-sulfamethoxazole, doxycycline, minocycline, and clindamycin are available for outpatient management of less severe skin and soft tissue infections, vancomycin (VAN) remains the cornerstone of therapy for serious MRSA infections requiring hospitalization, despite its slow bactericidal activity and clinical response.^{19–21} However, the efficacy of VAN is limited by increasing reports of infections caused by isolates with intermediate resistance to VAN (VISA), heterogeneous intermediate resistance to vancomycin (hVISA), and the emergence

of *vanA*-mediated, fully glycopeptide-resistant strains (VRSA).^{22–26} Furthermore, significant concerns surrounding the risk of nephrotoxicity associated with dose intensity as well as duration of therapy,²⁷ along with discrepancies in susceptibility results dependent on testing methodology,^{28,29} has generated interest in the newer Gram-positive agents.

Currently, five injectable anti-Gram-positive agents are approved and available in the US in addition to vancomycin (Table 2). However, due to a recent warning from the US FDA regarding increased risk in all-cause mortality associated with tigecycline use in pooled analysis of clinical trials, the use of tigecycline was not included in the latest published clinical practice guidelines for treatment of MRSA infections from the IDSA.³⁰

Although none of the available agents have demonstrated superiority against vancomycin for the primary outcome of clinical cure in randomized controlled trials of SSTIs, other advantages have been noted in previously published works.^{31,32} Linezolid was associated with a shorter duration of inpatient stay which resulted in a decrease in total direct medical costs compared to vancomycin.^{31–34} Moreover, linezolid was not associated with intravenous infusion reactions or nephrotoxicity.^{32,33}

In a randomized, open-label, comparator-controlled, multicenter, multinational study that included patients with suspected or proven MRSA, better overall outcomes at the test of cure were observed for a subgroup of patients who received linezolid for documented MRSA complicated skin and soft-tissue infection (cSSTI) compared to vancomycin (88.6% vs. 66.9%, $P < 0.001$).³⁵ This was further supported by a meta-analysis that reported that linezolid had a significantly higher odds of microbiologic eradication compared to vancomycin in cSSTI [odds ratio 2.90; 95% confidence interval (CI): 1.90–4.41].³⁴

Similarly, in a prospective, open label study evaluating daptomycin for complicated skin and skin structure infections compared with historical control of patients receiving vancomycin, no difference in clinical outcomes was reported.³⁶ However, quicker resolution of signs and symptoms associated with cSSTI was observed in a greater proportion of patients who received daptomycin compared to vancomycin (90% vs. 70%, $P < 0.01$).³⁶ Subsequently, a shorter median antibiotic-related length of stay was reported for the

**Table 2.** US Food and Drug Administration approved Gram-positive agents.

Agent	Drug class	Approval year	Comments
Linezolid ^{74,75}	Oxazolidinone	2000	Available in oral and intravenous formulations Coverage for Gram-positive organisms only Bacteriostatic Safety concerns: myelosuppression, optic neuritis, serotonin syndrome
Daptomycin ^{74–78}	Cyclic lipopeptide	2003	Available in intravenous formulation only Coverage for Gram-positive organisms only Bactericidal Safety concerns: creatinine kinase elevation, myopathy
Tigecycline ^{74,75,79}	Glycylcycline	2005	Available in intravenous formulation only Broad coverage Gram-positive Gram-negative (not including <i>Pseudomonas aeruginosa</i>) Anaerobic coverage Bacteriostatic Safety concerns: gastrointestinal intolerance, photosensitivity, injection site swelling
Telavancin ^{74,75,80}	Glycopeptide	2010	Available in intravenous formulation only Coverage for Gram-positive organisms only Bactericidal Safety concerns: nephrotoxicity, infusion-related reactions, QTc prolongation, coagulation test interference
Ceftaroline ^{81,82,83}	Cephalosporin	2011	Available in intravenous formulation only Broad coverage Gram-positive Gram-negative (selected enterobacteriaceae) Bactericidal Safety concerns: well-tolerated (nausea and headache most common) ⁸³

daptomycin versus the vancomycin arm (4 days vs. 8 days, respectively, $P < 0.01$).³⁶ More recently, a decision analytic model was developed to evaluate the cost-effectiveness of daptomycin, linezolid, and vancomycin in MRSA cSSTIs using Bayesian methods for evidence synthesis.³⁷ In this study, linezolid was cost-effective compared to vancomycin or daptomycin in the base-case as well as in most of the sensitivity analyses due primarily to decreased length of stay and decreased total direct costs for cSSTIs.³⁷

Logman, et al performed a network meta-analysis evaluating the pooled microbiological success rates for linezolid, daptomycin, telavancin, tigecycline, dalbavancin, and vancomycin.³⁸ The results provided a relative difference in microbiological cure rates using Bayesian meta-analysis techniques in the absence of direct head-to-head trials. Dalbavancin was reported to have a higher success rate [87.7% (95% Credible interval (CrI): 74.6%–95.4%) followed by linezolid (84.4% (95% CrI: 76.6%–90.6%), telavancin (83.5% (95% CrI:

73.6%–90.8%), daptomycin (78.1% (95% CrI: 54.6%–93.2%), vancomycin (74.7% (95% CrI: 64.1%–83.5%), and tigecycline (70.4% (95% CrI: 48%–87.6%)).³⁸ However, the meta-analysis did not include newer agents such as ceftaroline, ceftobiprole, or iclaprim.

In the past few years, several new compounds such as ceftobiprole, dalbavancin, oritavancin, and iclaprim have been examined for potential management of SSTIs. Here, we focus on the mechanism of action, microbiology, pharmacokinetics/pharmacodynamics, clinical experience, safety, and the potential role of iclaprim for SSTIs.

Iclaprim

Chemical structure

Iclaprim is a racemic mixture of 2 enantiomers³⁹ with an empiric formula of $C_{19}H_{22}N_4O_3$, a molecular weight of 354.40298 [g/mol], and an International Union of Pure and Applied Chemistry code: 5-[[[(2R)-2-cyclopropyl-7,8-dimethoxy-2H-chromen-5-yl]methyl]

pyrimidine-2,4-diamine.³⁹ Both enantiomers R-(1) and S-(1) are synthesized from the cyclopropyl homoallyl alcohols R-(6) and S-(6). The metamorphosis process included a Mitsunobu reaction and the acquisition of the diaminopyrimidine structure before the extraction of the desired chromene heterocycle.³⁹ The chromene ring then replaces the benzyl ring on the trimethoprim molecule (Fig. 1).

Mechanism of action

Iclaprim is a derivative of the 2,4-diaminopyrimidine that selectively inhibits DHFR, a critical enzyme that catalyzes the transfer of a hydride ion to 7,8-dihydrofolate (DHF) forming a 5,6,7,8-tetrahydrofolate (THF).^{40,41} The main function of THF is to maintain intracellular pools, cell growth and proliferation. Inhibition of the DHFR will prevent the reduction of DHF to THF which is responsible for the one carbon reaction that triggers the biosynthesis of nucleic acid and other metabolites.^{40,42} As a result, the interruption of DNA synthesis leads to cell death. However, due to a 10^5 difference in preferential binding affinity at the active sites between bacterial and human enzyme (<30% homology),⁴³ as well as amino acid sequence variation in the DHFR, iclaprim selectively inhibits bacterial DHFR with no activity against human DHFR.⁴⁴

Iclaprim possesses activity against Gram-negative strains very similar to TMP. However, it is much more potent against selected Gram-positive organisms including strains demonstrating TMP, methicillin, and vancomycin resistance. The structural features of the substrate-binding pocket may account for the observed activity against TMP-resistant strains. TMP resistance in *S. aureus* is due to a mutation of Phe98 to Tyr98, which disrupts the 4-amino group of TMP and subsequently its binding affinity.⁴⁵

Iclaprim differs in that it possesses a cyclopropyl group, which occupies a lipophilic pocket. It is hypothesized that perhaps the interaction between the lipophilic pocket and the cyclopropyl group pushes the diaminopyrimidine into the binding site, thus, bringing the molecule into closer proximity to form a hydrogen bond.¹⁴

In vitro activity

A variety of clinical isolates that is responsible for SSSI have been tested in vitro. Potent antibacterial activity has been observed against various Gram-positive organisms, including strains demonstrating TMP, β -lactam, methicillin, macrolide, fluoroquinolones, and glycopeptide resistance. It has also shown limited activity against Gram-negative organisms, similar to that of TMP. The proposed susceptibility breakpoints⁴⁶ for selected Gram-positive organisms are outlined in Table 3.

Gram-positive activity

Iclaprim was tested against 6,989 international clinical isolates of Gram-positive pathogens. A comparison of in-vitro activity between iclaprim and its comparators is summarized in Table 4.⁴⁷⁻⁴⁹ Iclaprim exhibits potent activity against most staphylococci isolates, as 90% of the isolates were inhibited with a minimum inhibitory concentration (MIC_{90}) of <0.012 $\mu\text{g/mL}$, including methicillin, vancomycin-intermediate, and vancomycin-resistant strains. The MIC for streptococci ranges from 0.03 $\mu\text{g/mL}$ for *S. pyogenes* to 4 $\mu\text{g/mL}$ for *S. viridans*. Iclaprim also shows excellent activity against β -hemolytic *Streptococcus* when compared with other agents. Elevation in MICs was observed for enterococci, with MIC_{90} of 4 $\mu\text{g/mL}$ and >8 $\mu\text{g/mL}$ for *Enterococcus faecalis* and *Enterococcus faecium*, respectively. As predicted,

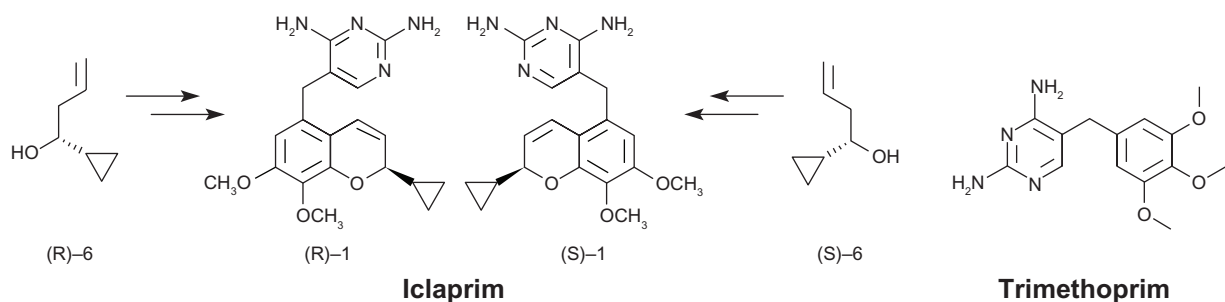


Figure 1. Iclaprim and trimethoprim chemical structures.

**Table 3.** Proposed Iclaprim susceptibility breakpoints.⁴⁶

Pathogens	MIC (µg/mL)		
	Susceptible	Intermediate	Resistant
<i>Staphylococcus aureus</i>	≤1	–	–
<i>Streptococcus pyogenes</i>	≤0.5	–	–
<i>Enterococcus faecalis</i>	≤0.5	1	≥2

E. faecalis is generally more susceptible when compared to *E. faecium*.

Gram-negative activity

Generally, iclaprim has similar activity against enterobacteriaceae, including ESBL, in comparison to TMP.^{50–52} Iclaprim is not active against *Pseudomonas* spp due to its intrinsic resistance to the benzyl-pyrimidines structure; thus, it was not tested. It also has variable activity against *Acinetobacter* spp and *Stenotrophomonas* spp,⁵¹ and minimal activity against selected anaerobes *Bacteroides distasonis*, *Bacteroides thetaiotaomicron* and *Fusobacterium nucleatum*.⁵³ It should be noted that iclaprim has also shown activity against *Legionella pneumophila* (MIC₅₀ = 0.03 µg/mL) and *Chlamydomphila pneumoniae* (MIC₅₀ = 0.5 µg/mL).

Pharmacokinetics

Iclaprim is parenterally administered and exhibits linear pharmacokinetics after a single dose in the range of 0.4 or 0.8 mg/kg over 30 minutes (min) or

Table 4. In vitro activity of iclaprim against selected Gram-positive organisms.^{47–49}

Pathogens	# of isolates	MIC ₅₀	MIC ₉₀	Range
MSSA	1513	0.06	0.12	0.008–4
MRSA	3003	0.06	0.12	≤0.004–8
VISA/hVISA	4	0.5	8	0.06–>8
VRSA	5	–	–	0.06–>8
<i>S. pyogenes</i>	604	0.015	0.03	≤0.004–0.12
<i>S. agalactiae</i>	204	0.12	0.25	0.15–0.5
<i>E. faecalis</i>	310	0.015	4	≤0.004–>8
<i>E. faecium</i>	303	2	>8	≤0.004–>8

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; VISA, vancomycin-intermediate *Staphylococcus aureus*; hVISA, heterogeneous VISA; VRSA, vancomycin-resistant *Staphylococcus aureus*.

Table 5. Comparative in vitro activity against selected Gram-negative organisms: MIC₉₀ (µg/mL).^{50–52}

Pathogens	# of isolates	ICL	TMP	TMP/SMX
<i>Haemophilus influenzae</i>	836	4	16	4
<i>Moraxella catarrhalis</i>	495	8	32	2
<i>Nisseria gonorrhoeae</i>	156	8	>64	–
<i>Escherichia coli</i>	50	>32	>32	>32
<i>Klebsiella</i> spp.	50	>32	>32	>32
<i>Enterobacter</i> spp.	25	4	1	0.25
<i>Serratia</i> spp.	23	>32	>32	>32
<i>Citrobacter</i> spp.	23	>32	>32	>32

Abbreviations: ICL, Iclaprim; TMP, Trimethoprim; TMP/SMX, Trimethoprim/Sulfamethoxazole (Bactrim®).

1.6 mg/kg over 60 min and multiple doses of 60 mg and 120 mg twice daily for 10 days.⁵⁴ At 0.8 mg/kg single dose infusion, the observed maximum concentration (C_{max}) was 867 ng/mL and 801 ng/mL, with associated area under the curve (AUC) values of 2150 ng/h/mL and 1980 ng/h/mL for males and females, respectively.^{55–57} Although the reported protein binding of iclaprim ranges from 92% to 94%,⁵⁸ the MICs of 40 methicillin-sensitive *S. aureus* and 38 MRSA isolates were not affected by the addition of human plasma when tested in vitro.⁵⁹ The average volume of distribution at steady states is 1.3–1.68 L/kg, indicating that it distributes well into tissues.^{55–57,60}

Iclaprim is metabolized by the liver, and eliminated as the inactive form predominantly through urine and feces, 70% and 20%, respectively.⁵⁴ The half-life is approximately 2–4 hours and the clearance is independent of dose.⁵⁴ There were no accumulations observed after repeated administration.⁵⁴

In an open label, parallel, single-dose study, the pharmacokinetics of iclaprim in 68 patients with varying degrees of renal or hepatic impairment, or obesity was determined.⁶¹ Varying degrees of renal impairment (6 mild, 6 moderate, 6 severe, and 6 end-stage renal disease) did not have significant impact on the pharmacokinetic parameters of iclaprim. A slight increase in AUC was observed in 8 patients with mild hepatic impairment. However, the AUC and C_{max} increased 2.5 and 1.4 fold, respectively, in 8 patients with moderate hepatic impairment.

A linear relationship was observed between body mass index and AUC ($P < 0.01$; $R^2 = 0.63$), particularly in severely obese patients (>40 kg/m²). Although



these results may suggest that dose adjustments should be considered in patients with moderate hepatic impairment and significantly obese patients, it should be noted that a relatively small number of patients was sampled for each category of impairment.

Pharmacodynamics

Iclaprim is an inhibitor of bacterial DHFR similar to TMP, but possesses higher binding affinity due to increased hydrophilic interactions with DHFR.⁶² At concentrations close to the minimum inhibitory concentrations (MIC), iclaprim demonstrates rapidly bactericidal concentrations against various species of streptococci and staphylococci. In a study comparing the minimum bactericidal concentration/minimum inhibitory concentration (MBC/MIC) ratio between iclaprim and vancomycin,⁴⁷ 100% and 60% of all MRSA isolates tested had a MBC/MIC ratio of ≤ 4 for iclaprim and vancomycin, respectively. For MSSA, 86% of the tested strains for iclaprim and vancomycin had a MBC/MIC ratio of ≤ 4 . Bactericidal activities of iclaprim for Group A and Group B streptococci with MBC/MIC of ≤ 4 were 45% and 65%, respectively, whereas all strains tested against vancomycin had MBC/MIC of ≥ 32 . Regarding enterococci, 20% of *E. faecalis* and 40% of *E. faecium* had MBC/MIC of ≤ 4 for iclaprim. Meanwhile, both strains of enterococci had MBC/MIC of ≥ 32 for vancomycin.⁴⁷

Time-kill kinetic assays were used to determine the comparative bactericidal activity of iclaprim, vancomycin, and TMP against *S. aureus*, VISA, *S. pneumoniae*, and *Enterococcus* species. Iclaprim achieved a 99.9% kill for *S. aureus* by 3–5 hours at the concentrations of 2- to 8-fold above the MIC. Vancomycin had slower bactericidal activity against *S. aureus* with only 90% kill after 16 hours at concentrations 16-fold above the MIC.⁶³ Iclaprim also had post-antibiotic effect for 1 hour for *E. coli* and at least 2 hours against *S. aureus* and *S. epidermidis*. The post-antibiotic effect was time- and concentration-dependent.⁶³

To determine its synergy potential, iclaprim was tested in combination with folate inhibitors and other antimicrobial agents with different mechanisms of action.⁶⁴ Using checkerboard methodology, iclaprim was tested in combination with 32 other agents against selected Gram-positive, Gram-negative, and anaerobic organisms, including reference strains. Of note, synergism was observed against

S. aureus, including strains demonstrating methicillin resistance when iclaprim was used in combination with sulfamethoxazole. Neither synergism nor antagonism was noted in combination with the other antimicrobial agents against all isolates tested.

Resistance

Since the discovery of the first clinical use of diaminopyrimidine, development of TMP resistance rates were minimal compared to other drug classes (eg, approximately 4% of *S. aureus*).⁶⁵ On average, the calculated frequency of resistance in *S. aureus* was observed at a rate below 10^{-10} . Resistance induction study showed that TMP had a high resistance rate after 4–5 passages when exposed to sub-inhibitory concentrations of tested antimicrobials. Resistance to TMP is mediated mainly by a point mutation of the Phe98Tyr gene.⁶⁶ In a resistance induction study involving iclaprim, the development of resistance in both MSSA and MRSA strains were very low even after 15 passages at sub-inhibitory concentration. Resistant colonies could not be extracted at the resistance frequency of 10^{-10} . In addition, ultraviolet mutagenesis studies showed that the frequency of resistance for *E. coli* could not be detected at a rate of 10^{-10} for iclaprim.^{66,67} Iclaprim appears to have low potential for resistance based on all data that were presented. Despite these observations, the reversal of DHFR inhibitors have been observed in vitro with the augmentation of thymidine, resulting in bacterial uptake of exogenous thymidine, circumventing DHFR inhibition.⁶⁸ Given these reports, there may be some concern regarding the role of iclaprim in purulent infections, given the high concentrations of thymidine in human pus.⁶⁹

Clinical studies

Due to the promising activity of iclaprim in the treatment of cSSSI, the US FDA subsequently granted fast-tracked approval for iclaprim in Phase III trials. Two Phase III trials, the Arpida Skin and Skin Structure Infection Study 1 and 2 (ASSIST-1 and ASSIST-2), evaluated the efficacy and safety of iclaprim compared to linezolid for the management of cSSTI in 991 adult patients. The patients were randomized to receive 0.8 mg/kg of iclaprim every 12 hours or 600 mg of linezolid every 12 hours intravenously.

ASSIST-1⁷⁰ was a double-blind, randomized, multicenter study conducted to compare the efficacy of



intravenous iclaprim versus linezolid in cSSSIs. A total of 497 patients were randomized to receive iclaprim 0.8 mg/kg every 12 hours intravenously (N = 249) or linezolid 600 mg intravenously every 12 hours (N = 248) for 10 to 14 days. The primary end point was clinical cure at the test-of-cure (TOC) visit (7 to 14 days post-treatment). Patients who received co-administration of other antimicrobials were excluded from the study. However, the addition of aztreonam and/or metronidazole was allowed for the management of Gram-negative infections when warranted. The clinical cure rate in the intention-to-treat (ITT) population was 83.1% and 88.7% [95% CI: -11.7% to 0.6%] for iclaprim and linezolid, respectively, at the TOC visit. In the per protocol (PP) population, the clinical cure rate was 94.7% in the iclaprim arm and 99.1% in the linezolid arm [95% CI: -8.4% to -1.0%]. In both studied groups, *S. aureus* was the most commonly isolated organism (73.8%), of which, 22.2% were MRSA. The observed eradication rate for all bacteria was 85.7% and 92.6%; for *S. aureus* was 86.9% and 89.9%; and for MRSA was 84.7% and 85.3%, in the iclaprim and linezolid arms, respectively.

A second, multicenter, randomized Phase III clinical trial, ASSIST-2,⁷¹ compared the efficacy of intravenous iclaprim versus linezolid for the treatment of cSSSIs. No difference was reported in the ITT and PP populations, for iclaprim and linezolid (81.3% vs. 81.9% [95% CI: -7.5% to 6.3%] and 90.0% vs. 96.4% [95% CI: -11.6% to -1.5%]), respectively. *S. aureus* was the predominant organism isolated in this study (62.6%), with MRSA encompassing half of those isolates.

The algorithm for the ASSIST-1 and ASSIST-2 trials excluded patients who received co-administration of other antibacterial agents, in which the outcomes

were defined as indeterminate as described in the protocol. However, upon review by the FDA, there were additional patients who received prohibited antibiotics and were not excluded from the analysis. As such, in an analysis conducted by the FDA which changed the outcomes of those patients from cure to indeterminate (Table 6), the lower bound of the 95% confidence interval exceeded the non-inferiority margin of 10% in most of the ITT and PP populations.⁴⁶ As such, iclaprim failed to achieve FDA non-inferiority status against linezolid for the management of cSSTI.

Safety

Overall, iclaprim appears to be well tolerated in the combined Phase III trials. However, it appears to be associated with mild-moderate gastrointestinal disturbances, with the highest reported adverse event of elevated transaminases (7.2%), followed by headache (6.4%), nausea (6.0%), diarrhea (5.8%), and constipation (5.4%).⁴⁶

Iclaprim was reported to prolong the QTc interval prior to Phase III studies. Several safety concerns were raised from the formal electrocardiography results in the Phase I studies.⁷² Iclaprim at a dose of 3.2 mg/kg showed evidence of transient QTc prolongation but without any serious events reported. In the combined ASSIST-1 and ASSIST-2 trials, iclaprim demonstrated a higher mean change in QTc and threshold of >30 ms for both Day 1 and Day 4 compared to linezolid. Furthermore, QTc prolongation exceeding the threshold of >60 ms occurred more commonly (approximately twice the rate) in patients who received iclaprim versus linezolid. No serious cardiac events such as torsade de pointes or ventricular arrhythmias were noted due to QTc prolongation with iclaprim 0.8 mg/kg

Table 6. FDA analyses of Phase III studies of iclaprim versus linezolid in complicated skin and skin structure infections.

	ASSIST-1 (N = 497)		ASSIST-2 (N = 494)	
	Iclaprim	Linezolid	Iclaprim	Linezolid
Clinical Cure Rate: ITT [95% CI]	80% (201/249) -8.0% [-14.3%, -1.7%]	88.7% (220/248)	80.1% (199/251) -0.1% [-7.3%, 7.0%]	80.7% (193/243)
Clinical Cure Rate: PP [95%CI]	92.2% (190/206) -6.8% [-11.4%, -3.0%]	99.1% (211/213)	88.5 (183/209) -5.8% [-11.6%, 0.5%]	94.9% (182/195)
Microbiological cure at TOC	81.9% (113/138)	91% (131/144)	77.2% (115/149)	79.4% (127/160)
Eradication rate: <i>S. aureus</i>	83.9% (78/93)	89.8% (97/108)	82.2% (60/73)	84.6% (66/78)
Eradication rate: MRSA	77.8% (35/45)	94.4% (34/36)	74.3% (55/74)	75% (60/80)

Abbreviations: ASSIST, Arpida Skin and Skin Structure Infection Study; ITT, intent-to-treat; CI, confidence interval; PP, per protocol; TOC, test-of-cure; MRSA, methicillin-resistant *Staphylococcus aureus*.



every 12 hours for 14 days. Given the potential for QTc prolongation with iclaprim use, caution should be exercised when other agents with a similar potential for QTc prolongation are used in conjunction.

Conclusion

The controversies surrounding the management of SSTIs alongside the changing landscape of the organisms involved in these infections present significant challenges to clinicians. In particular, the rapid spread of CA-MRSA as a causative pathogen of community SSTI has changed the empiric approach to treating such infections substantially.^{6–10} Moreover, recent data suggests that the use of broad spectrum antibacterials with Gram-negative and anaerobic coverage is unnecessary in patients with cellulitis and abscesses without complicating factors.¹³

Iclaprim is a new diaminopyrimidine that demonstrates potent bactericidal activity against Gram-positive organisms, including MSSA, MRSA, VISA, VRSA, and strains harboring TMP resistance. Given its limited activity against Gram-negative organisms, iclaprim can be considered for management of cellulitis and abscess in the absence of complicating factors, from a microbiologic perspective. Moreover, it may have a role in immunocompromised hosts for directed therapy against selected pathogens given its potent bactericidal activity. However, it should be noted that published randomized clinical trials is lacking, and this paper is limited by discussion of iclaprim clinical experience generated from data in abstract form. Furthermore, its failure to achieve non-inferiority status in the two Phase III studies against linezolid raises serious concerns regarding iclaprim's role in the management of cSSTIs.

As of December, 2009, Acino Holding Ltd. acquired 100% of the shares of Arpida Ltd., including all assets, data, and intellectual property rights relating to iclaprim.⁷³ Subsequent to the complete response letter in January, 2009, the FDA issued new draft guidance in August of 2010 recommending new clinical end-points and study populations in a newly defined indication, acute bacterial skin and skin structure infections. It is possible that Acino may be able to pool data from the previous two Phase III trials along with new analysis in preparation for resubmission. Pending the final language on the draft guidance, it is plausible that perhaps only one additional study may be required. As

such, the role of iclaprim in the management of SSTIs remains to be determined.

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