ABSTRACT

Background: PTK796 (PTK) is a novel antimicrobial agent that undergoes clinical development. PTK activity was evaluated against methicillin-resistant S. aureus (MRSA) and -resistant S. aureus (MSSA), including multiple-resistance strains from documented hospital-acquired (HA) infections and community-associated (CA) infection isolates.

Methods: S. aureus were collected from bloodstream, skin and skin structure, CA and HA pneumonia in USA (52 sites) and Europe (11, 11 laboratories). The two broth microdilution method (SIM, www.sim.com) was utilized (9 comparator) applying fresh Mueller-Hinton media when testing PTk and tigecycline. Cobblestone did was used to confirm MRSA, CA-MRSA genotypes (USA500 [12] and USA300 [5]) were identified by PPRG and SCCmec typing and PVL genes.

Results: PTK MIC values for all strains were ≤0.5 μg/ml. PTK (MIC90, 0.25 μg/ml), tigecycline (MIC90, 0.12 μg/ml) and oxacillin (MIC90, 0.5 μg/ml) were all susceptible. Similar results were observed among HA-MRSA and CA-MRSA isolates.

Conclusions: PTK activity was active against S. aureus, displaying a narrow potency range (0.12–0.5 μg/ml). Consistent PTK activity was observed, regardless of geographic origin, and genotypic or resistances subsets.

INTRODUCTION

Resistance to currently available antimicrobial classes has increased markedly; and safe and effective treatment options are needed for clinical use against numerous Gram-positive and-negative bacterial pathogens. Staphylococcus aureus is the most common Gram-positive species associated with human infections, including serious and invasive diseases. Strains of methicillin-resistant S. aureus (MRSA) are commonly resistant to other antimicrobials and the often causes difficult decisions for clinical practitioners when selecting treatment.

Healthcare-associated (HA-MRSA) infections have long been known as a serious problem among very ill patients and have been very problematic regarding treatment. Some therapeutic options have required intensive monitoring of adverse side effects such as toxicity, nephrotoxicity, severe colitis and muscle weakness. In more recent years, community-associated MRSA (CA-MRSA) has come to the forefront of clinical consideration and has also become a serious therapeutic concern. CA-MRSA commonly causes wound infections and it is recognized as the most problematic pathogen in the healthcare environment and is responsible for many skin and skin structure infections (SSSI), which may advance to bacteremia.

This study was performed to evaluate the in vitro antimicrobial activity of PTK796, a novel tetra cyclic-like (aminomethyl) pyridine, agent, against methicillin-resistant S. aureus (MRSA) and MSSA from medical centers located in Europe and the United States (USA). PTK796 is a broad-spectrum agent with proven efficacy in animal models for treating clinically prevalent infections caused by Gram-positive and Gram-negative bacteria, including those with multidrug resistance (MDR). Phase III trials will determine the safety and efficacy of PTK796 in the treatment of S. aureus, many of which will be caused by MRSA and MSSA.

RESULTS

Overall, 99.1% of the isolates were inhibited by ≤0.5 μg/ml of PTK796, including all MSSA, HA-MRSA from Europe and CA-MRSA from the USA. The MIC values for PTK796 were ≤0.5 μg/ml for isolates tested in this collection (Table 1).

Slightly higher PTK796 MIC values were noted among HA-MRSA isolates from USA compared to European isolates (Table 2). The highest PTK796 MIC values (2 μg/ml) were observed among two HA-MRSA strains from two different medical centers in the USA. PTK796 was slightly more active against strains from the USA (MIC90, 0.25 μg/ml; 96.6% susceptible) compared to those from Europe (MIC90, 0.5 μg/ml; 96.6% susceptible). Tigecycline was two-fold more active (MIC 90, 0.03 μg/ml) against USA isolates compared to the European collection (MIC90, 0.25 μg/ml). In this collection, doxycycline showed elevated MIC values.

The in vitro activity established in this study coupled with the decreased susceptibility to doxycycline documented among MRSA isolates from Europe.

In conclusion, PTK796 is a promising antimicrobial agent for the treatment of serious MDR S. aureus infections.

MATERIALS AND METHODS

Bacterial isolates: A total of 325 non-duplicate isolates of S. aureus from documented patient infections were collected from medical centers located in the USA and Europe. Approximately equal numbers of isolates were collected from each region and included MSSA (54), HA-MRSA (94) and CA-MRSA (224). The primary medical center provided the species identification and a reference laboratory (JMI Laboratories, North Liberty, Iowa, USA) confirmed the susceptibility with formalin-fixed plates and tube end point agar dilution tests (Reme1, Leneba, KS, USA), when needed. Antimicrobial susceptibility testing: All isolates were tested for antimicrobial susceptibility using the reference agar dilution panels with cation-adjusted Mueller-Hinton broth purchased by JMI Laboratories. Testing was performed according to the broth microdilution method as described in the Clinical and Laboratory Standards Institute (CLSI, M07-A8, 2009) using freshly prepared Mueller-Hinton broth (Becton, Dickenson and Company, Franklin Lakes, New Jersey, USA). PTK796 and nine comparator agents, including direct or related class agents (doxycycline and tigecycline) were tested. Interpretive criteria for MIC values of comparison agents were those of the CLSI (M07-S10, 2010) or USA-FDA criteria (Tigecycline). Consensus quality control (QC) testing of S. aureus ATCC 29213 was performed per M07-A8 [2009] and ranges found in M07-S10 (2010).

Molecular characterization of CA-MRSA PCR amplification of Panton-Valentine leukocidin (PVL) genes (nap-PV and icaA-PV) was performed with primers published elsewhere. The isolates were characterized for the types of SCCmec gene cassette using a multiplex PCR strategy. The mecA gene was amplified as part of the multiplex PCR to serve as an internal control. PCR products were separated on 2% agarose gel in TAE buffer on Criterion Sub-cell GT system (Bio-Rad, Hercules, CA) and stained with ethidium bromide. SCCmec types were assigned based on the number and sizes of the amplicons obtained. Pulsed-field gel electrophoresis (PFGE) band patterns of strains were compared to those of USA300, USA400 and other USA clones previously published.

This study was supported by Paratek Pharmaceuticals.

CONCLUSIONS

In Vitro Evaluation of PTK796 Activity Tested against Staphylococcus aureus, Including Hospital- and Community-Associated MRSA Strains from the USA and Europe

DJ BIEDENBACH, RE MENDES, HS SADER, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

REFERENCES