Telavancin (TLV) Is More Bactericidal Than Vancomycin (VAN) against Both Extracellular and Intracellular (THP-1 Macrophages) Staphylococcus aureus with Different Resistance Phenotypes

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ABSTRACT

Background: TLV is a novel lipoglycopeptide (presently in late clinical trial evaluation) with marked bactericidal activity against S. aureus, including strains resistant to conventional glycopeptides. We compare here TLV and VAN activity against extracellular and intracellular S. aureus with different resistance phenotypes.

Methods: MICs were determined by microdilution in Mueller-Hinton broth (for methicillin-susceptible S. aureus (MSSA) or in Mueller-Hinton broth supplemented with 2% sodium chloride for methicillin-resistant S. aureus (MRSA). Bacteria in cell culture medium (extracellular) or in THP-1 infected macrophages (intracellular; see Barcia-Macay et al., Antimicrob Agents Chemother. 2005;50:841-851) were exposed for up to 24 hours to VAN or TLV at increasing extracellular concentrations.

Results: The table shows the MICs of VAN and TLV together with the changes in cfu from the initial inoculum measured extracellularly and in THP-1 macrophages at a concentration equal to the human Cmax (VAN; 50 mg/L; TLV 90 mg/L [total drug]). Extracellularly, TLV displayed a larger bactericidal effect than VAN, reaching the limit of detection within 6 hours for MSSA and MRSA. Intracellularly, VAN was almost static, while TLV showed a bactericidal effect, which, however, was less pronounced for vancomycin-resistant S. aureus (VISA) compared with other strains.

Methods: MICs were determined by microdilution in Mueller-Hinton broth supplemented with 2% sodium chloride for MRSA. Extracellular activity was evaluated by performing killing curve experiments in Roswell Park Memorial Institute medium supplemented with 10% fetal calf serum (Barcia-Macay et al. Antimicrob Agents Chemother. 2006;50:841-851).

RESULTS

1. EXTRACELLULAR ACTIVITY

MICs were determined by microdilution in Mueller-Hinton broth supplemented by 2% sodium chloride for MRSA. Extracellular activity was evaluated by performing killing curve experiments in Roswell Park Memorial Institute medium supplemented with 10% fetal calf serum (Barcia-Macay et al. Antimicrob Agents Chemother. 2006;50:841-851).

2. INTRACELLULAR ACTIVITY

Intracellular activity was produced by a 1-hour incubation with serum-opsonized bacteria (4 bacteria/THP-1 macrophage), washing with gentamicin for 1 hour, and reincubation in fresh medium containing the tested antibiotic. The killing of cell protein was determined by plating cell lysates (Barcia-Macay et al. Antimicrob Agents Chemother. 2006;50:841-851).

CONCLUSIONS

1. TLV proved bactericidal toward both the extracellular and intracellular forms of S. aureus, irrespective of resistance phenotype.

2. SIMILARITY OF DOSE RESPONSE TOWARD MSSA AND MRSA: MAY BE RELATED TO THE MULTIPLE MODES OF ACTION OF TLV DESCRIBED BY HIGGINS AND COLLEAGUES (ANTIMICROB AGENTS CHEMOTHER. 2005;49:1127-1134)

3. VAN was bacteriostatic toward the extracellular form of S. aureus and slowly bactericidal toward the intracellular form.

INTRODUCTION

Selecting an appropriate treatment for S. aureus infections currently involves 2 major issues: 1. Increasing resistance to the available semi-synthetic agents for strains of MRSA, vancomycin-intermediate S. aureus (VISA), and vancomycin-resistant S. aureus (VRSA) narrows the choice of antibiotics.

2. The capacity of S. aureus to survive and multiply within eukaryotic cells protects it from the bactericidal action of many antibiotics and is probably associated with the persistence or recurrent character of infections (Loyez, Tetsu Microbiol. 2008;54:314-333).

TLV is a rapidly bactericidal semi-synthetic glycopeptide, which, in contrast to VAN:


The aim of this study was to compare the extracellular and intracellular activity of VAN and TLV toward staphylococci harboring different resistance phenotypes.

METHODS

1. TLV proved bactericidal toward both the extracellular and intracellular forms of S. aureus, irrespective of resistance phenotype.


3. VAN was bacteriostatic toward the extracellular form of S. aureus and slowly bactericidal toward the intracellular form.