Efficacy of Telavancin in a Rabbit Model of Aortic Valve Endocarditis Due to Methicillin-Resistant \textit{Staphylococcus aureus} or Vancomycin-Intermediate \textit{Staphylococcus aureus}

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The activities of telavancin and vancomycin were compared in vitro and in the rabbit model of aortic valve endocarditis against a methicillin-resistant \textit{Staphylococcus aureus} strain, COL, and a vancomycin-intermediate \textit{S. aureus} (VISA) strain, HIP 5836. Telavancin was bactericidal in time-kill studies at a concentration of 5 \mu{g}/ml against both COL and HIP5836. Vancomycin was bacteriostatic at 5 \mu{g}/ml and bactericidal at 10 \mu{g}/ml against COL and was bacteriostatic at 10 \mu{g}/ml against VISA strain HIP 5836. Compared to untreated controls, a twice-daily regimen of 30 mg/kg of telavancin reduced mean aortic valve vegetation titers of the COL strain by 4.7 \log_{10} CFU/g after 4 days of therapy and sterilized 6/11 vegetations compared to 3.4 \log_{10} CFU/g with 3/10 vegetations sterilized for a regimen of twice-daily vancomycin, 30 mg/kg; these differences were not statistically significant. Telavancin was significantly more effective than vancomycin in the VISA model, producing a 5.5 \log_{10} CFU/g reduction versus no reduction in CFU with vancomycin. In experiments comparing 2-day regimens of telavancin at 30 mg/kg and 50 mg/kg twice daily, organisms were rapidly eliminated from vegetations, but the effect was not different between the two doses. These results suggest that telavancin may be an effective treatment for endocarditis and other serious staphylococcal infections accompanied by bacteremia, including infections caused by \textit{staphylococci} not susceptible to vancomycin.

Telavancin (formerly known as TD-6424) is an investigational lipoglycopeptide derivative of vancomycin (4, 5). It is more rapidly bactericidal than vancomycin in vitro, exhibits concentration-dependent killing, and is active against strains with reduced susceptibility to vancomycin (6, 7). This in vitro activity is likely due to the novel, multiple mechanisms of action of telavancin, including effects on membrane permeability as well as inhibition of peptidoglycan synthesis (4). In animal models of soft-tissue infection, telavancin is efficacious and more potent than vancomycin or linezolid (3). Telavancin is in phase 3 clinical trials as a once daily agent for treatment of serious infections caused by gram-positive pathogens. The purpose of the present study was to compare the efficacy of telavancin to vancomycin against antibiotic-resistant \textit{Staphylococcus aureus} in a rabbit model of aortic valve endocarditis.

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MATERIALS AND METHODS

\textbf{Bacterial strains.} In separate experiments, endocarditis was established with either of two \textit{S. aureus} isolates: the homogeneous, highly methicillin-resistant \textit{S. aureus} (MRSA) strain COL or a vancomycin-intermediate \textit{S. aureus} (VISA) strain, HIP 5836, which is a methicillin-resistant (nafcillin MIC, 16 \mu{g}/ml), \beta-lactamase-producing clinical isolate from a patient in New Jersey (originally designated strain 992) (2, 9).

\textbf{Susceptibility studies.} MICs were determined by the standard microdilution method in cation-supplemented Mueller-Hinton broth with an inoculum of 2 \times 10^{5} CFU/ml after a 24-h incubation at 35°C. Time-kill studies were performed using a 1:100 dilution of an overnight culture in cation-adjusted Mueller-Hinton broth to compare the bactericidal activities of telavancin and vancomycin; 50-\mu{l} samples of culture were taken after 0, 4, and 24 h of incubation at 37°C, serially diluted 10-fold, and inoculated onto blood agar. Colonies were counted after incubation for 24 h at 37°C.

\textbf{Endocarditis model.} The animal studies were approved by the Committee on Animal Research of the University of California, San Francisco. Endocarditis of the aortic valve was established in 2- to 3-kg New Zealand White rabbits by positioning a catheter across the aortic valve and securing it in place for the duration of the experiment. Animals were infected 48 h after insertion of the catheter by intravenous injection of 1 ml of bacterial suspension containing \approx 10^{6} CFU in 0.9% saline. Experiments were conducted to compare the activities of telavancin and vancomycin in animals infected with either COL or the VISA strain HIP 5836 and to assess dose-response with telavancin.

For comparison of telavancin and vancomycin, rabbits were infected with one of the two strains and then were randomly assigned to one of three groups: untreated controls; a 4-day treatment regimen of telavancin administered intravenously at 30 mg/kg twice a day; or a 4-day regimen of vancomycin administered intravenously at 50 mg/kg twice a day. Therapy was begun 16 to 18 h after bacterial challenge.

Experiments performed to assess the dose-response of telavancin were conducted with rabbits infected with the COL strain. Rabbits were randomly assigned to one of the following three groups: untreated controls; a 2-day treatment with telavancin administered intravenously at a dose of 30 mg/kg twice daily; or a 2-day treatment with telavancin administered twice daily at a dose of 50 mg/kg. Therapy was begun 16 to 18 h after bacterial challenge.

Controls were sacrificed approximately 18 h after infection to determine the number of organisms present prior to therapy. Rabbits assigned to treatment groups were sacrificed 18 to 24 h after the last dose of telavancin or vancomycin. Aortic valve vegetations were harvested and weighed. Samples were homogenized in 0.5 ml of 0.9% saline and quantitatively cultured onto blood agar. After incubation at 37°C for 24 h, colonies were counted and the result was expressed as \log_{10} CFU per gram of vegetation. The lower limit of detection by this method is approximately 1 \log_{10} CFU/g. Vegetations in which no organisms were detected were scored as sterile and assigned a value of 0 \log_{10} CFU/g for purposes of data analysis. Differences between mean vegetation titers of the several groups were tested for statistical significance by analysis of variance.
followed by Student’s t test adjusted for multiple comparisons by Bonferroni correction.

Serum drug concentrations of telavancin were determined from blood samples obtained from the marginal ear vein at 1 h and 12 h after dosing. Serum was collected and frozen at −70°C. Telavancin was assayed by the manufacturer using a validated liquid chromatography/mass spectrometry/mass spectrometry method (3). Telavancin has a longer elimination half-life in humans (7 to 9 h) (8) than in rabbits (1 to 2 h) (data not shown). Telavancin administered to rabbits at 30 mg/kg twice a day was estimated to achieve similar 24-h area-under-the-curve (AUC) and time above the MIC as a clinical dose of 7.5 mg/kg (30-min infusion) in humans (8). Pharmacokinetic data for vancomycin have been determined previously (1). Vancomycin has a half-life of 80 min in rabbits, and a regimen of 30 mg/kg administered intravenously twice a day produces serum concentrations (total drug) 1 h after dosing of 29 μg/ml, which is similar to that seen in humans (1).

RESULTS

Susceptibility studies. The MICs of telavancin were 1 μg/ml against the MRSA strain COL and 4 μg/ml against the VISA strain HIP 5836. Vancomycin MICs were 2 and 8 μg/ml, respectively. Telavancin was bactericidal (≥3 log10 decrease in CFU at 24 h of drug exposure) in time-kill studies at a concentration of 5 μg/ml against both COL and HIP 5836 (Fig. 1). Vancomycin was bacteriostatic at 5 μg/ml and bactericidal at 10 μg/ml against COL. It did not inhibit growth of the VISA strain, HIP 5836, at 5 μg/ml and was bacteriostatic at 10 μg/ml.

Endocarditis model. The mean ± standard deviation values for serum concentration in infected rabbits at 1 h after a 30-mg/kg dose and a 50-mg/kg dose of telavancin were 102 ± 11 (n = 6) and 133 ± 24 μg/ml (n = 6) (P < 0.025), respectively. The mean concentration 12 h after the 30-mg/kg dose was 0.4 ± 0.6 (n = 11). Telavancin concentrations at 12 h following the 50-mg/kg dose were not assayed.

Telavancin reduced vegetation titers of COL by a mean of 4.7 log10 CFU/g compared to untreated rabbits (Table 1), a statistically significant decrease. Vancomycin produced a mean reduction of 3.4 log10 CFU/g, a decrease that was not significantly different from either controls or telavancin-treated rabbits. Six of 11 telavancin-treated rabbits had sterile vegetations, compared to 3 of 10 vancomycin-treated rabbits (P = 0.38, Fisher exact test).
Vancomycin had no effect on the vegetation titers of rabbits infected with the VISA strain HIP 5836, with the organism burden in vegetations being slightly higher than in the controls. None of the rabbits treated with vancomycin had sterile vegetations, and four died during treatment. Telavancin produced an approximately 5.5 log₁₀ reduction in CFU compared to the controls. Four rabbits had sterile vegetations, and one died during the treatment period.

In the 2-day dose escalation studies comparing telavancin administered intravenously at a dose of 30 mg/kg and 50 mg/kg twice a day, both regimens significantly reduced the overall mean vegetation titers compared to untreated controls (Table 1). The two dosage regimens had similar efficacy. Notably, the number of residual organisms in vegetations after 2 days and 4 days of exposure to telavancin were similar, suggesting that most of the killing occurs early during therapy.

**DISCUSSION**

Telavancin is an investigational lipoglycopeptide with multiple mechanisms of action (4, 5). In vitro it is more active than vancomycin, and its spectrum of activity includes vancomycin-intermediate and -resistant staphylococci and enterococci. This expanded spectrum is thought to be due to the presence of a hydrophobic side chain on the vancosamine sugar of the molecule that interferes with critical membrane functions (10).

The antibacterial activities of telavancin and vancomycin in vivo in the rabbit model of aortic valve endocarditis resembled their relative in vitro activities. The MICs of telavancin were half those of vancomycin against the MRSA strain COL and the VISA strain HIP 5836. In time-kill studies telavancin was bactericidal against both strains, whereas vancomycin was only bactericidal at the 10 μg/ml concentration against the COL strain. Telavancin was more active than vancomycin for endocarditis caused by either strain. Rapid sterilization of vegetations occurred within 2 days of treatment. These results suggest that telavancin may be an effective treatment for endocarditis as well as other serious staphylococcal infections, including those caused by staphylococci not susceptible to vancomycin.

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