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Comparative Efficacies of Telavancin and Vancomycin in Preventing Device-Associated Colonization and Infection by *Staphylococcus aureus* in Rabbits[▽]

Rabih O. Darouiche,[1]* Mohammad D. Mansouri,[1] and Marlowe J. Schneidkraut[2]

Infectious Disease Section and Center for Prostheses Infection, Michael E. Debakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas,[1] and Astellas Pharma US, Inc., Deerfield, Illinois[2]

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Telavancin is an investigational lipoglycopeptide antibiotic that is active against gram-positive pathogens. In an in vivo rabbit model, subtherapeutic (15-mg/kg) and therapeutic (30- or 45-mg/kg) doses of telavancin were demonstrated to be noninferior and superior to vancomycin (20 mg/kg), respectively, for preventing subcutaneous implant colonization and infection by *Staphylococcus aureus*.

Estimated annual infection rates in the United States associated with the most commonly used medical devices range from 3% to 8% for central venous catheters, 10% to 30% for bladder catheters, and 5% to 10% for fracture fixation devices (2). Since more than 37 million of these devices are inserted annually, device-associated infections affect millions of patients and, as such, are a major medical and economic issue (2).

Telavancin is an investigational lipoglycopeptide, with activity against clinically relevant gram-positive pathogens, including *Staphylococcus aureus* (8, 9, 15), which is one of the most important bacterial species implicated in the pathogenesis of device-related infections (2). In clinical trials, telavancin has been shown to be efficacious for the treatment of complicated skin and skin structure infections (17–19) as well as hospital-acquired pneumonia (14). The present study provides preclinical evidence that telavancin may also be more efficacious for the prevention of device colonization and infection by gram-positive pathogens than vancomycin. We used vancomycin rather than a β-lactam antibiotic as a control prophylactic agent for the following three reasons. (i) Vancomycin is currently the most commonly used agent for perioperative systemic prophylaxis when inserting surgical implants, regardless of the patient's status of methicillin-resistant *Staphylococcus aureus* colonization. (ii) Vancomycin has been reported to be superior to some β-lactam antibiotics in preventing certain postoperative infections. For instance, in a randomized, double-blinded trial by Maki and colleagues, the preoperative prophylactic use of vancomycin in patients embarking on cardiac and vascular operations was more protective against infection than the use of cefazolin or cefamandole. As a result, the authors suggested the use of vancomycin as an antibiotic prophylaxis in prosthetic valve replacement and prosthetic vascular graft implantation to reduce the risk of implant infection (12). (iii) Although both vancomycin and β-lactam antibiotics share with telavancin a rather similar mechanism of action (inhibition of cell wall synthesis), it was important to determine if the two structurally related glycopeptide compounds, vancomycin and telavancin, indeed differ in their efficacies.

This study was conducted with prior approval from the appropriate Institutional Animal Care and Use Committee (IACUC). Modifications to a previously described rabbit model of subcutaneous implant colonization and infection by *S. aureus* were used in these studies (3, 4, 6). In a similar rabbit model that compared vancomycin to dalbavancin, a compound closely related to telavancin, we demonstrated a statistically insignificant trend for lower rates of device colonization in the dalbavancin group than in the vancomycin group. Telavancin was obtained from Theravance, Inc. (South San Francisco, CA), vancomycin from Hospira (Lake Forest, IL), and water with 5% dextrose (D5W) from IVX Animal Health (St. Joseph, MO). In vitro bacterial susceptibility to telavancin and vancomycin was tested, in triplicate, by standard macrodilution (1). We used specific-pathogen-free, 4- to 7-month-old female New Zealand White rabbits, with a body mass of 3 to 4 kg each (Myrtle's Rabbitry, Thomson Station, TN). Anesthesia was induced by intramuscular injection of xylazine at 6 mg/kg and acepromazine at 2 mg/kg and maintained via inhalation of 0.5% to 2% isoflurane for the duration of the surgery.

Anesthetized animals were randomly assigned to one of five treatment groups (nine rabbits each) and injected, intravenously, over a period of ~2 min, with a single dose of sterile D5W (control), vancomycin (20 mg/kg), or one of three doses of telavancin (15, 30, or 45 mg/kg). Based on previously reported efficacy and exposure data for rabbits (11), this telavancin dose range of 15 to 45 mg/kg for rabbits corresponds to 50% to 150% of the human area under the concentration-time curve-equivalent dose (HED) of 10 mg/kg (10), which is also the recommended human clinical dose (18). The vancomycin dose used in this study was similar to those used in prior rabbit studies, including this particular model (3). Following a surgical procedure described previously (3), six 2-cm-long segments of seven French triple-lumen polyurethane vascular catheters were implanted subcutaneously in the back of each animal, for a total of 54 devices per nine rabbits in each group. The implanted devices were inoculated on the surface directly with 10^5 CFU (50-μl total inoculum in Trypticase soy broth) using

* Corresponding author. Mailing address: Center for Prostheses Infection, Baylor College of Medicine, 1333 Moursund Avenue, Suite A221, Houston, TX 77030. Phone: (713) 799-5088. Fax: (713) 799-5058. E-mail: rdarouiche@aol.com.

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strain P1 of *S. aureus*, a methicillin-sensitive *S. aureus* (MSSA) clinical isolate associated with device-related infections that has been used by us and others for studies of medical device colonization (3, 6). The mean MIC and minimal bactericidal concentration of the MSSA P1 strain used in this study were 0.25 μg/ml and 1 μg/ml for telavancin, respectively, and 1 μg/ml and 8 μg/ml for vancomycin, respectively. Surgical wounds were closed, and the animals were observed closely in the operating room until they achieved sternal recumbency. The analgesic/anti-inflammatory agent ketoprofen (3 mg/kg) was given intramuscularly to each rabbit immediately following surgery and as needed thereafter. The animals were monitored daily for signs of pain, distress, erythema, local infection, and sepsis.

One week postsurgery, all rabbits were anesthetized and humanely sacrificed. Implanted catheter segments were recovered in a sterile fashion and cultured based on a previously described sonication technique (13, 16). Swab cultures were collected from the soft tissues adjacent to the implantation site or wound drainage, while blood samples were collected by cardiac puncture. The surgical site swabs as well as the blood samples were cultured using standard techniques (4, 5).

Device colonization was defined as growth of the inoculated *S. aureus* strain from the sonication culture of the explanted device. Device-related infection was defined as any growth of the inoculated strain from both the sonication culture of the explanted device and the swab culture of any soft tissue collection or wound site discharge. Explanted devices were sonicated in 2 ml of normal saline, and 200 μl of the sonicate and subsequent dilutions were cultured. As a result, the detectability limit was 10 CFU.

The sample size was determined based on our previous experience with this animal model, which showed a 19% reduction in the rate of infection when using dalbavancin rather than vancomycin (3). In this study, we sought a similar magnitude of reduction (19%) in the frequency of infection when using telavancin compared to vancomycin with a power of 80% and a type I error of 5%. Frequencies of device colonization and local device-related infections in the five treatment groups were compared using a two-tailed Fisher's exact test at an alpha level of 0.05 (Stata statistical software, version 8.2; StataCorp, College Station, TX).

The mean MIC and minimal bactericidal concentration of the MSSA P1 strain used in this study were 0.25 μg/ml and 1 μg/ml for telavancin, respectively, and 1 μg/ml and 8 μg/ml for vancomycin, respectively. Blood cultures derived from all groups were sterile, indicating the absence of device-related bacteremia. The frequencies of device colonization and device-associated infection by the inoculated *S. aureus* strain were significantly higher in the control group than in each of the four treatment groups (Table 1). Preoperative systemic administration of telavancin reduced the rates of *S. aureus* device colonization and device-associated infection in a dose-related fashion. A subtherapeutic dose of telavancin (15 mg/kg), representing a HED of 4.8 mg/kg, was noninferior to vancomycin at 20 mg/kg in preventing device colonization and device-related infections. Single therapeutic doses of telavancin (30 mg/kg or 45 mg/kg), representing HEDs of 9.6 and 14.4 mg/kg, respectively, were superior to vancomycin (20 mg/kg) at preventing device colonization and device-related infections (Table 1).

TABLE 1. Rates of device colonization and device-related infection by *S. aureus*

Treatment group (dose)	Device colonization rate (%) (no. of devices colonized/ total no. of devices)	Device-related infection rate (%) (no. of devices infected/total no. of devices)
D5W control	100 (48/48)[a]	100 (48/48)[a]
Vancomycin (20 mg/kg)	52 (28/54)[b]	52 (28/54)[b]
Telavancin (15 mg/kg)	39 (21/54)[b,c]	35 (19/54)[b,c]
Telavancin (30 mg/kg)	11 (6/54)[b,d]	9 (5/54)[b,d]
Telavancin (45 mg/kg)	11 (6/54)[b,d]	11 (6/54)[b,d]

[a] Data for analysis were available from only 48 implanted devices because one animal expired prematurely from an unknown cause.
[b] *P* value of <0.0001 versus the control.
[c] *P* value of >0.1 versus vancomycin.
[d] *P* value of <0.0001 versus vancomycin.

The expanding use of some surgically implanted devices, coupled with an increase in the number of device-associated infections, has encouraged the assessment of newer approaches for preventing such serious and potentially life-threatening infections (20). This is particularly true in this era, as vancomycin, an antibiotic that is poorly active against biofilm-embedded bacteria, is becoming widely regarded as being less optimal than previously perceived. Previous studies have suggested that telavancin may have superior antimicrobial activity against staphylococcal biofilms compared to the antimicrobial activity of vancomycin. Vancomycin is usually considered to possess time-dependent inhibitory activity. However, unlike other glycopeptide antibiotics, telavancin has been reported to possess concentration-dependent activity (7), and this finding was supported by the results of our study. It is possible that telavancin could be more effective than vancomycin in preventing the formation of biofilm because of its concentration-dependent activity. Since the first step in the formation of biofilm is bacterial attachment, it is possible that the high concentration of telavancin may be instrumental in inhibiting the early stage of bacterial attachment and subsequent biofilm formation, whereas vancomycin acts over a longer period of time. We implemented several measures to reduce or eliminate possible biases, including selection bias and information bias. As indicated, rabbits were randomly selected to receive different doses of telavancin or vancomycin. Furthermore, each device was assigned a number independent of the type of antibiotic treatment given to the rabbit with the implanted device. Devices were cultured, and bacterial colonies were counted based on the assigned numbers in a blinded fashion. The data from this in vivo study suggest that preoperative intravenous administration of telavancin may constitute an effective clinical approach to reduce or prevent staphylococcal colonization and infection of surgical implants.

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