Evaluation of the extracellular and intracellular activities (human THP-1 macrophages) of telavancin versus vancomycin against methicillin-susceptible, methicillin-resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus

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Objectives: To compare extracellular and intracellular activities of telavancin (versus vancomycin) against Staphylococcus aureus (MSSA, MRSA, VISA and VRSA).

Methods: Determination of cfu changes (3–24 h) in culture medium and in macrophages at concentrations ranging from 0.01 to 1000 × MIC.

Results: Extracellularly, telavancin displayed a fast, concentration-dependent bactericidal activity against all strains. The concentration–effect relationship was bimodal for MSSA and MRSA [two successive sharp drops in bacterial counts (0.3–1 × MIC and 100–1000 × MIC) separated by a zone of low concentration dependency]. When compared at human total drug $C_{\text{max}}$ (vancomycin, 50 mg/L; telavancin, 90 mg/L) towards MSSA and MRSA, telavancin caused both a faster and more marked decrease of cfu, with the limit of detection (>5 log decrease) reached already at 6 versus 24 h for vancomycin. Intracellularly, the bactericidal activity of telavancin was less intense [−3 log (MSSA) to −1.5 log (VRSA) at $C_{\text{max}}$ and at 24 h]. A bimodal relationship with respect to concentration (at 24 h) was observed for both MSSA and MRSA. In contrast, vancomycin exhibited only marginal intracellular activity towards intraphagocytic MSSA, MRSA and VISA (max. −0.5 log decrease at 24 h and at $C_{\text{max}}$).

Conclusions: Telavancin showed time- and concentration-dependent bactericidal activity against both extracellular and intracellular S. aureus with various resistance phenotypes. The data support the use of telavancin in infections where intracellular and extracellular S. aureus are present. Bimodality of dose responses (MSSA and MRSA) could indicate multiple mechanisms of action for telavancin.

Keywords: lipoglycopeptide, Gram-positive, bactericidal, phagolysosomes, concentration dependence

Introduction

Treatment for Staphylococcus aureus infections faces two major issues: (i) recurrent and relapsing character (convincingly associated with the capacity of this organism to survive and multiply within eucaryotic cells) and (ii) narrowing choice of available agents due to increased emergence of resistance. Therefore, new agents remaining active against multi-resistant strains and demonstrating bactericidal activity against both extracellular and intracellular bacteria are needed. This is probably all the more important since pharmacodynamic analyses of vancomycin successes and failures in patients with severe infections suggest that considerably higher drug dosages than anticipated may be needed for successful therapy.
Telavancin, a hydrophobic derivative of vancomycin,\textsuperscript{7} displays a more intense bactericidal activity than vancomycin against \textit{S. aureus} and other Gram-positive organisms and remains active against vancomycin-resistant organisms.\textsuperscript{8,9} This has been related to its multiple modes of action, which, beyond inhibition of bacterial cell wall synthesis, also includes disruption of bacterial membrane integrity.\textsuperscript{10\textsuperscript{14}} Telavancin is effective in various animal models of difficult-to-treat staphylococcal infections and in biofilms,\textsuperscript{12\textsuperscript{16}} and is in clinical development.\textsuperscript{17,18} Moreover, telavancin accumulates within alveolar macrophages,\textsuperscript{19} which could be useful for controlling intracellular infections.

In the present study, we compared the extracellular and intracellular activities of telavancin and vancomycin against \textit{S. aureus}, using strains with different resistance phenotypes towards \(\beta\)-lactams and vancomycin, and cultured murine and human macrophages. The antibacterial responses were analysed over a wide range of extracellular concentrations (pharmacological analysis) and discussed in terms of total and free concentrations as they can be observed clinically in humans.\textsuperscript{20,21}

Materials and methods

Cells and cell cultures

Human (THP-1) macrophages (grown in suspension) and murine (J774) macrophages (grown as monolayers) were cultured exactly as described previously.\textsuperscript{22\textsuperscript{25}}

Bacterial strains and MIC determinations

The following strains were used: (i) ATCC 25923 (fully susceptible); (ii) ATCC 29213 (\(\beta\)-lactamase producing MSSA); (iii) ATCC 35591 (MRSA with heterogeneous resistance to oxacillin) and ATCC 43300 (MRSA with heterogeneous resistance to oxacillin);\textsuperscript{26} (iv) NRS23 (HIP08926) and NRS52 (HIP09737) [MRSA with intermediate level of vancomycin resistance (VISA)]; and (v) VRS1 (HIP11714 or Michigan strain)\textsuperscript{27} and VRS2 (HIP11983 or Pennsylvania strain)\textsuperscript{28} [MRSA with high level of resistance to vancomycin (VRSA)]. MICs were measured by microdilution in Muller–Hinton broth,\textsuperscript{22,25} supplemented by 2% NaCl for MRSA [US Clinical Laboratory Standards Institute (CLSI), Wayne, PA].

Determination of antibiotic activity against extracellular \textit{S. aureus}

Kill curve experiments were performed in the culture medium of macrophages (containing 10% foetal calf serum)\textsuperscript{29} and for control purposes also in Muller–Hinton broth, according to previously published and validated methods.\textsuperscript{25,29} In brief, all samples (diluted as needed) were prepared in a final volume of 1 mL, and 50 \(\mu\)L was used for seeding standard Petri dishes. After 24 h incubation at 37°C, colonies were counted using an automated detector\textsuperscript{29} with validation of vancomycin resistance (VISA); and (v) VRS1 (HIP11714 or Michigan strain)\textsuperscript{27} and VRS2 (HIP11983 or Pennsylvania strain)\textsuperscript{28} [MRSA with high level of resistance to vancomycin (VRSA)]. MICs were expressed as the per cent increase in the medium/cell activity ratio; therefore, corresponding to a net release of the enzyme from cells. Control cells (no antibiotic added) and cells exposed to telavancin showed the same increase (6.1 ± 0.3%) up to telavancin concentrations of 150 mg/L, but there was a 25.2 ± 2.5% increase for cells incubated with 500 mg/L telavancin, denoting a significant level of cell toxicity. Vancomycin (250 mg/L) was without significant effect compared to control cells.

Confocal and electron microscopy

This was performed exactly as described previously for adherent and non-adherent cells.\textsuperscript{22,25}

Materials

Telavancin hydrochloride for microbiological evaluation (purity > 90%) was supplied in powder form by Theravance Inc, South San Francisco, CA, USA. Because of its low solubility, stock solutions (1–10 mg/L in water) were prepared with extensive shaking (at least 30 min) and carefully checked for absence of undissolved material. Although suggested by the manufacturer, no DMSO and/or acid addition was made since these interfered with macrophage viability. Vancomycin and linezolid were procured as the corresponding branded products registered in Belgium for parenteral use (VANCOCIN\textsuperscript{\textregistered} from GlaxoSmithKline; ZYVOXID\textsuperscript{\textregistered} from Pfizer). MSSA and MRSA strains were obtained from the American Type Culture Collection (ATCC), Manassas, VA, USA; and VISA...
and VRSA isolates from the Network on Antimicrobial Resistance in S. aureus (NARSA) at Focus Technologies, Inc., Herndon, VA, USA. Cell culture or microbiology media were from Invitrogen Ltd, Paisley, UK, and from BD Diagnostics Systems (formerly DIFCO Inc.), Sparks, MD, USA. Other reagents were of analytic grade and purchased from E. Merck AG (Darmstadt, Germany) or Sigma-Aldrich-Fluka (St Louis, MO, USA).

Results

Susceptibility testing

MICs/MBCs (mg/L) of vancomycin were 1/1 and 1/1 for MSSA ATCC 25923 and ATCC 29213; 2/4 and 2/2 for MRSA ATCC 33591 and ATCC 43300; 4/4 and 4/4 for VISA NRS23 and NRS52 (MICs for VRSA VRS1 and VRS2 were >128 and 16). MICs/MBCs (mg/L) of telavancin were 0.5/0.5 for MSSA (ATCC 25923 and ATCC 29213), 0.5/1 and 0.5/0.5 for MRSA (ATCC 33591 and ATCC 43300), 0.5/0.5 for VISA (NRS23 and NRS52), and 4/8 and 2/8 for VRSA (VRS1 and VRS2); the MICs observed for those two VRSA are the same as those reported recently by another group of investigators;36 for VRS2; however, the original publication37 reported a value of 0.5 mg/L. For all strains, no marked difference was seen when MICs were determined in broth adjusted to pH 5.5 (to mimic the phagolysosomal environment) versus pH 7.3.

Extracellular activity

Figure 1 shows the kinetics of activity of vancomycin and telavancin towards extracellular S. aureus exposed to three selected concentrations, namely the MIC, 10× MIC and a concentration mimicking the reported human total drug Cmax.20,21 Vancomycin always acted slowly, with a marked influence of the concentration at 24 h only. For all three strains tested, a bactericidal effect (3 log cfu decrease) was obtained only at a concentration of 10× the MIC or higher, and after an incubation time of ~20 h at 10× the MIC and of 15 h at Cmax. In contrast, telavancin (i) was more concentration dependent; (ii) produced a bactericidal effect for MSSA ATCC 25923 and ATCC 29213, and for MRSA ATCC 33591 within 18 h at 1× the MIC only; (iii) was bactericidal at Cmax for all strains (including the two VRSA strains) within 2 h (MSSA ATCC 25923) to 10 h (MRSA ATCC 43300 and VRS1); (iv) caused apparent complete eradication at Cmax within 6 h for MSSA ATCC 25923, MRSA ATCC 33591 and NRS52, and at 24 h for MSSA ATCC 29213 and MRSA ATCC 43300. Towards VISA NRS23 and the two VRSA, telavancin was bacteriostatic at its MIC, but caused a 4.5 log decrease at Cmax.

Figure 2 shows the results observed against MSSA ATCC 25923 using a wide range of drug concentrations (0.01 to 1000× MIC) and after 3 or 24 h of incubation. At 3 h (left panel), telavancin exerted an antibacterial effect that developed in a bimodal fashion, with a first decrease in cfu to reach a plateau at about 2.5 log below the original inoculum for concentrations ranging from 1 to 10× MIC, followed by a second decrease to a value close to the limit of detection at 300× MIC or higher. In contrast, vancomycin caused only a modest decrease in cfu even at the largest concentration tested. At 24 h (right panel), telavancin caused a 4 log cfu decrease at the MIC, and the limit of detection was reached at a concentration of 10× MIC, making the bimodal character of the response difficult to observe. Vancomycin also exhibited a dose-dependent bactericidal activity, but higher multiples of MICs (3- to 10-fold) were needed to achieve similar killing effects.

The concentration dependency of telavancin extracellular activity towards S. aureus was further examined for all remaining strains at the same time points (Figure 3; data obtained with strain ATCC 25923 shown in Figure 2 are included for comparison). At 3 h (left panels), (i) an apparent static effect was seen for MRSA, VISA and VRSA strains at a telavancin concentration close to the MIC; (ii) the bimodal response with respect to the concentration was clearly seen for MRSA [with the first plateau (1.5–2.5 log decrease) in the 1–100× MIC range as for MSSA ATCC 29213], but almost not for VISA and not for VRSA (linear decrease in cfu as a function of the drug concentration). For all strains (except MSSA ATCC 25923 which was more susceptible), a bactericidal effect (3 log cfu decrease) at 3 h required concentrations of 300–1000× the MIC. At 24 h (right panels), a bactericidal effect was obtained for concentrations of ~0.85–2× MIC (0.4–1 mg/L) for MSSA and MRSA, and of ~10–44× the MIC (5–22 mg/L) for VISA and VRSA. The limit of detection was obtained at concentrations spanning from 10× MIC (MSSA ATCC 25923) to 250× MIC (NRS23). To check for a potential interference of calf serum in the results shown above, kill curves (3 and 24 h) were repeated for MSSA (ATCC 25923 and ATCC 29213) and MRSA (ATCC 33591 and ATCC 43300) using Muller–Hinton broth. Results not significantly different from those shown in Figure 3 (including the bimodality of the response at 3 h) with an excellent correlation between the two sets of data [linear regression parameters for all data points included in the comparison (n = 77; values below the detection limit were excluded): slope, 0.981 ± 0.02 (95% CI: 0.940–1.024); R² = 0.967; P < 0.0001].

Intracellular activity (infected macrophages)

We first examined whether our model of S. aureus infected J774 and THP-1 macrophages developed with MSSA ATCC 2592322,25 could be used with the other strains included in this study. In all cases, the intracellular growth could be monitored, and the extracellular growth prevented by the addition of gentamicin (10× MIC for MRSA and VISA), or linezolid (1× MIC for VRSA) when no glycopeptide was added (controls). Intracellular bacteria were unambiguously observed in the macrophages by confocal and/or electron microscopy (data not shown). As discussed previously,25 cultures maintained in the absence of antibiotic (or with the lowest concentrations [0.01× MIC] of the antibiotics tested) showed a larger bacterial growth [about 2–3 log cfu increase (VRSA strains) over the original inoculum], which was partly due to extracellular bacteria, but without gross deleterious effect on macrophages, as assessed by the measurement of total cell protein [no significant change (J774 macrophages) or modest reduction (23.5% ± 16.8; P = 0.017; n = 24 for THP-1 cells) between infected cultures exposed to telavancin at 0.01 and 100× MIC, respectively].

The kinetics of intracellular activities of vancomycin (left panel) and telavancin (right panel) was compared towards MSSA ATCC 25923 in THP-1 macrophages exposed to the three selected concentrations (MIC, 10× MIC and the Cmax) used previously for assessing extracellular activities (Figure 4).
Figure 1. Kinetics of activity of vancomycin and telavancin against the extracellular forms of *S. aureus*. The graphs show the variation in the number of cfu per mL of culture medium upon incubation of *S. aureus* strains [MSSA: ATCC 25923, ATCC 29213; MRSA: ATCC 33591, ATCC 43300; VISA: NRS23, NRS52; VRSA (telavancin only): VRS1, VRS2] for up to 24 h with increasing concentrations of vancomycin and telavancin [corresponding to 1× MIC, 10× MIC, and the human $C_{max}$ (50 mg/L for vancomycin\(^2\); 90 mg/L for telavancin\(^3\)]. The initial inoculum varied from $10^{5.99}$ to $10^{6.06}$ cfu/mL. Results are given as means ± standard deviation ($n = 3$; when not visible, SD are smaller than the symbols). The thick dotted line corresponds to a static effect (no change from the initial inoculum); the grey dotted line shows the decrease in cfu (3 log) considered as denoting a bactericidal effect;\(^3\) the dotted line at −5 log corresponds to the lower limit of detection.
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Figure 2. Concentration–effect relationship of the activity of vancomycin and telavancin against the extracellular forms of S. aureus. The graphs show the variation in the number of cfu per mL of culture medium upon incubation of S. aureus MSSA ATCC 25923 for 3 h (left) or 24 h (right) with increasing concentrations of vancomycin and telavancin (ranging from 0.01 to 1000× MIC). The initial inoculum was 10⁶ cfu/mL. Results are given as means ± standard deviation (n = 3; when not visible, SD are smaller than the symbols). The thick dotted line corresponds to a static effect (no change from the initial inoculum); the thin dotted line at –5 log shows the limit of detection.

Vancomycin did not prevent bacterial growth at its MIC, became static at 10× its MIC and achieved intracellular killing (–1.3 log) at its Cmax only after 24 h (only marginal effects were seen at 3 and 6 h). In contrast, telavancin was rapidly bactericidal at all 3 concentrations tested, achieving a 2 log decrease within 6 h at its Cmax. No further decrease in bacterial counts, however, was seen upon longer exposure to telavancin.

The concentration dependency of the extracellular activities of vancomycin and telavancin was then examined at 24 h for all strains over a 0.01 to 1000× MIC concentration range. Figure 5 shows the data obtained with THP-1 human macrophages. For both antibiotics, concentration–dependent effects were seen, but with significant differences in the concentrations needed for static and maximal effects. Thus, a bacteriostatic effect was obtained with vancomycin at 3–10× MIC or higher, but already at 1× MIC with telavancin (except for VRSA which required higher concentrations). At higher concentrations of telavancin, a first plateau was then reached at about 1–1.5 log cfu below the original inoculum for extracellular concentrations ranging from 1–5 to 50–100× MIC. This plateau was followed by a second decrease in the number of cfu for MSSA and MRSA at concentrations ranging between 100 and 1000× MIC. For VISA and VRSA, only a first plateau at about 1.5 log decrease from the original inoculum was observed. Similar results were obtained with telavancin in J774 macrophages (not shown).

Discussion

This study shows that telavancin displays a fast bactericidal activity against extracellular as well as intraphagocytic forms of S. aureus, including MRSA, VISA and VRSA strains. These properties contrast with the overall behaviour of vancomycin, which displays a slower bactericidal activity towards extracellular bacteria, and a bacteriostatic effect only towards intracellular bacteria.

Telavancin shares with vancomycin the pharmacophore that allows its binding to the bacterial d-Ala-d-Ala motif, causing inhibition of the peptidoglycan biosynthesis. In telavancin, however, it also displays a decylaminooethyl side chain that confers membrane destabilization properties in bacteria at higher concentrations. This may explain why telavancin (i) acts more quickly and is more bactericidal than vancomycin against vancomycin-susceptible strains; (ii) displays bimodal concentration effects towards MSSA and MRSA, but almost linear concentration effects towards VISA and VRSA, since these are expected to be poorly susceptible (VISA) or resistant (VRSA) to the d-Ala-d-Ala binding-mediated inhibition of peptidoglycan synthesis. For the VRSA strains, the loss of the action mediated by binding to d-Ala-d-Ala may also explain the higher MICs and larger MBC/MIC ratio of telavancin, compared with other strains, since the membrane destabilization-mediated mode of action, which should be the only one to operate in VRSA, appears to require larger concentrations.

The intracellular activity of telavancin was weaker than its extracellular activity (as is the case for all antibiotics examined in our models so far). Yet, and in sharp contrast with vancomycin, telavancin nevertheless exhibited a bactericidal activity (defined here as a 3 log decrease from the original inoculum by analogy to what is commonly accepted to categorize an antibiotic as bactericidal and as proposed previously) for all strains tested. This effect is unlikely to result from a direct contact of extracellular telavancin with intraphagocytic S. aureus, since we could exclude any gross membrane destabilization of macrophages in our model. Interestingly, bimodal concentration-effect curves were clearly seen for intraphagocytic MSSA and MRSA, and to some extent VISA, suggesting that the multiple modes of action of telavancin observed against the extracellular forms of these strains are also operating in the intracellular environment. We know that telavancin penetrates macrophages in vitro and in vivo. Future studies will therefore need to critically examine key cellular pharmacokinetic/pharmacodynamic parameters of telavancin such as its subcellular disposition, bioavailability and local expression of activity.

The present data obtained in vitro may not be extrapolated to the in vivo situation without caution. First, we only used two types of immortalized macrophages with poor or no host defences against intracellular infection, but this was to obtain a true pharmacological evaluation of telavancin (the activity of which seems less influenced by the immune status of the host than that of vancomycin or linezolid). Second, the persistence of viable intracellular bacteria even after extended exposure to large concentrations of telavancin needs to be critically examined, but this phenomenon is not specific to telavancin. Third, we used exposure to constant drug concentrations, which is not in line with the projected clinical use of telavancin.

While all these limitations clearly call for the development of more refined, dynamic in vitro models, the design of our experiments, nevertheless, allows for potentially useful discussions with respect to dose–effect relationships. Telavancin is bactericidal (using the criterion of 3 log cfu decrease) within 24 h for the extracellular forms of all strains at concentrations ranging from 0.7 (MSSA ATCC 25923) to 22 mg/L (VISA NR523, the least susceptible strain in our study). In vivo pharmacodynamic models suggest that telavancin efficacy is best predicted by the AUC/MIC ratio. Applying this to our conditions, the AUC needed to reach a 3 log cfu decrease within 24 h...
The graphs show the variation in the number of cfu per mg cell protein upon incubation of *S. aureus* MSSA ATCC 25923 for up to 24 h with increasing concentrations of vancomycin and telavancin (corresponding to 1× MIC, 10× MIC and the human C\(_{\text{max}}\) (50 mg/L for vancomycin\(^{21}\); 90 μg/mL for telavancin\(^{25}\)). The initial inoculum was \(10^6\) cfu/mg of cell protein. Results are given as means ± standard deviation (n = 3; when not visible, SD are smaller than the symbols). The thick dotted line corresponds to a static effect (no change from the initial inoculum).

\[\text{AUC} = 24 \times C_{3\log\text{ decrease}} \text{ (mg/L)},\]\n
using the data of Figure 3] would be around 10 for MSSA ATCC 25923 and ATCC 29213, around 12 and 25 for MRSA ATCC 39591 and ATCC 43300, around 125 and 500 for VISA NRS23 and NRS52, and around 600 and 1200 for VRSA VRS2 and VRS1. The typical human dose of 10 mg/kg of telavancin (used in the current clinical trials\(^{17,18}\)) yields a total drug AUC of ~900 mg·h/L,\(^{20}\) suggesting that a bactericidal effect will be easily be obtained for MSSA, MRSA and VISA strains and for VRS2, and will be close to being obtained for VRS1. But this does not take into account the high protein binding of telavancin (93%).\(^{20}\) For most antibiotics, including teicoplanin, another glycopeptide with high protein binding, it is generally agreed that pharmacokinetic/pharmacodynamic indices such as AUC/MIC ratios must use free drug concentrations only.\(^{40,41}\) If this was also the case for telavancin, we should conclude that bactericidal effects may never be obtained for VISA and VRSA strains in vivo, since the minimal AUC needed, based on our data but corrected for protein binding, might be far above what the projected clinical dosage could yield. Recent *in vitro* studies, however, failed to demonstrate a marked influence of serum on the killing capabilities of telavancin,\(^{36}\) suggesting that using only free drug concentrations to calculate a given target attainment rate would underestimate the real potency of the drug. It is also of interest that kill curves performed in Mueller–Hinton broth or in the cell culture medium (which contains 10% foetal bovine serum) showed no significant differences.

Given these caveats, the present study suggests that telavancin has the potential to display useful activity against *S. aureus* in those infections where not only eradication of extracellular bacteria but also the control of intracellular forms is critical. Reaching both goals may allow decreasing persistence and recurrence, two well-known features of many staphylococcal infections. These may include skin and soft tissues infections, or endocarditis, two diseases in which telavancin efficacy has already been successfully studied.\(^{12,14,17,18}\)
Telavancin extracellular and intracellular activities

![Graphs showing concentration-effect relationship of the activity of telavancin against S. aureus strains](image)

**Figure 5.** Concentration-effect relationship of the activity of telavancin against the intracellular forms of *S. aureus* in a model using human THP-1 macrophages. The graphs show the variation in the number of cfu per mg cell protein upon incubation of *S. aureus* strains [MSSA: ATCC 25923, ATCC 29213; MRSA: ATCC 33591, ATCC 43300; VISA: NRS23, NRS52; VRSA (telavancin only); VRS1, VRS2] with vancomycin (left) or telavancin (right) at increasing extracellular concentrations (ranging from 0.01 to 1000× MIC) for 24 h. The initial inoculum varied between $10^6.11$ and $10^6.37$ cfu/mg of cell protein. Results are given as mean±standard deviation ($n=3$; when not visible, SD are smaller than the symbols). The thick dotted line corresponds to a static effect (no change from the initial inoculum).

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Transparency declaration

None to declare.

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