Posters

New antimicrobials – before and after entering clinical development

P532 Antimicrobial activity of telavancin against *Enterococcus faecalis*, *E. faecium* and *E. avium*: results from a European surveillance programme (2007)

T. Fritsche, H. Sader, R. Jones (North Liberty, US)

Objectives: To evaluate the potency of telavancin (TLV) against enterococcal isolates (*Enterococcus faecalis* [EF], *E. faecium* [EFM] and *E. avium* [EAV]) collected as part of a European surveillance protocol for 2007. TLV is an investigational, intravenous, semi-synthetic, rapidly bactericidal lipoglycopeptide that is broadly active against both aerobic and anaerobic Gram-positive bacteria. The agent has been evaluated in two Phase 3 complicated skin and skin structure infection clinical trials.
Methods: Non-duplicate clinical isolates (919 total; see Table) of EF (579), EFM (318) and EAV (12) were submitted from 26 medical centres in Europe participating in TLV surveillance. Identifications were confirmed by the central monitor and all isolates were susceptibility tested using CLSI broth microdilution methods.
Results: Among the comparators, TLV was the most potent agent tested against *Enterococcus* spp. (EF and EFM; MIC50 values, 0.25 and 0.06 mg/L, respectively; see Table) compared with vancomycin (VAN; 1 and 1 mg/L), daptomycin (1 and 2 mg/L), levofloxacin (1 and >4 mg/L), and linezolid (1 and 1 mg/L). TLV was 4-fold more active (MIC50) than VAN against EF and 16-fold more active against EFM (only 15.4% of EFM had TLV MIC values of >1 mg/L compared with 29.6% having VAN MIC values >4 mg/L). Overall, 9.7% of tested enterococci were VAN-resistant, including 1.0% of EF and 25.8% of EFM; TLV remained ⩾16-fold more potent (MIC50) than VAN against these resistant EFM strains. Among the comparators, only daptomycin and linezolid were uniformly active against all enterococci (>99% susceptible), followed by teicoplanin (92.4%) and VAN (88.9%). All but one strain of EAV were inhibited by ⩽0.06 mg/L of TLV.

Table. Antimicrobial activity of telavancin against year 2007 enterococcal isolates

Organism (N)	MIC (mg/L)		Cumulative % inhibited at MIC (mg/L)				
	50%	90%	⩽0.06	0.12	0.25	0.5	1
EF (579)	0.25	0.5	1	22	84	99	99
VAN-susceptible (573)	0.25	0.5	1	23	84	100	–
VAN-resistant (6)	>2	>2	0	0	0	0	0
EFM (318)	0.06	2	66	79	80	80	85
VAN-susceptible (224)	0.06	0.12	82	99	100	–	–
VAN-resistant (82)	2	>2	18	21	21	22	40
EAV (12)	0.06	0.06	92	92	92	92	100

EAV, *Enterococcus avium*; EF, *E. faecalis*; EFM, *E. faecium*; VAN, vancomycin.

Conclusions: Based on MIC50 potencies, TLV was the most active agent tested against European (2007) *Enterococcus* spp. isolates, and inhibited 94.0% of strains at ⩽1 mg/L, whereas only 88.9% were inhibited by ⩽ 4 mg/L of VAN (current breakpoint). Continued monitoring for resistance emergence in enterococci and other Gram-positive pathogens will be critical in assessing the long-term efficacy of this promising agent.

P533 Activity of telavancin tested against *viridans* group and beta-haemolytic streptococci, and multidrug-resistant *Streptococcus pneumoniae*

T. Fritsche, G. Moet, H. Sader, R. Jones (North Liberty, US)

Objectives: To evaluate the activity of telavancin (TLV) tested against *viridans* group streptococci (VGS, five species), beta-haemolytic streptococci (BHS) and *Streptococcus pneumoniae* (SPN), including multidrug-resistant strains. TLV is a novel, rapidly bactericidal lipoglycopeptide active against Gram-positive pathogens, including resistant subsets, and has been evaluated in complicated skin and skin structure infection clinical trials.
Methods: The activity of TLV was compared with those of other antimicrobial classes using reference broth microdilution (CLSI, M7-A7; Mueller-Hinton broth supplemented with 2–5% lysed horse blood) methods tested against 1005 streptococci (100 each of five VGS species; 100 each of Lancefield Groups B, C and G BHS; and 205 SPN, including multidrug-resistant patterns [>3 classes]) recovered from global surveillance programmes.
Results: Among tested VGS, 99.8% had TLV MICs of ⩽0.06 mg/L. All MIC50 and MIC90 values for *S. anginosus*, *S. constellatus*, *S. mitis* and *S. oralis* were 0.03 mg/L; *S. intermedius* showed an elevated MIC90 (0.06 mg/L) and the highest TLV MIC (0.25 mg/L). Serogroups B, C and G BHS had the same modal TLV MIC (0.03 mg/L), but MIC90 results varied from 0.03 mg/L for Group C BHS to 0.06 mg/L for Groups B and G BHS. All BHS were inhibited by ⩽0.12 mg/L. Against SPN, TLV had a pronounced modal MIC at 0.015 mg/L (also MIC50 and MIC90) and 99.5% of results were either 0.008 or 0.015 mg/L (highest MIC). No difference in the TLV MIC90 (0.015 mg/L) was observed, but the MIC50 was slightly lower (0.008 mg/L) for two resistance phenotypes (penicillin-nonsusceptible [30 strains] and erythromycin-resistant [10 strains]). TLV MIC results did not correlate with mechanisms of resistance found for β-lactams, macrolides, tetracyclines, fluoroquinolones and trimethoprim/sulfamethoxazole. Overall, >99% of TLV MIC results occurred within three dilution steps (0.015–0.06 mg/L) for the tested streptococci.
Conclusions: TLV was found to be highly potent against prevalent VGS, BHS and SPN. All isolates were inhibited by ⩽0.06 mg/L TLV, with two exceptions (0.2%): one group G BHS at 0.12 mg/L and one *S. intermedius* at 0.25 mg/L. These results demonstrate that TLV may be an excellent therapeutic candidate for serious infections caused by these pathogenic organisms.

P534 Antimicrobial activity of telavancin and comparator agents tested against recently isolated (2007) European *Staphylococcus aureus* and coagulase-negative staphylococci

T. Fritsche, D. Biedenbach, H. Sader, R. Jones (North Liberty, US)

Objectives: Telavancin (TLV) is an investigational, novel, rapidly bactericidal lipoglycopeptide that is broadly active against Gram-positive pathogens, and has completed complicated skin and skin structure infection clinical trials. Given concerns over the rapid emergence of resistance among staphylococci, including community-acquired strains, we compared the potency of TLV versus other antimicrobials against contemporary oxacillin-susceptible (OX-S) and OX-resistant (OX-R) *Staphylococcus aureus* (SA) and coagulase-negative staphylococci (CoNS) collected as part of a European antimicrobial resistance surveillance programme.
Methods: Consecutive, non-duplicate patient isolates (n = 2834) were submitted from 26 medical centres in Europe (10 countries), Turkey and

Israel during 2007 (2202 SA [OX-R, 29.3%], 632 CoNS [OX-R, 76.1%]) and susceptibility tested using CLSI (M7-A7) broth microdilution methods.

Results: Compared with OX-S SA, TLV MIC90 values varied by one dilution in OX-R SA (0.12 versus 0.25 mg/L, respectively; see Table), but was unchanged for OX-R CoNS (0.25 mg/L); all isolates were inhibited by ⩽0.5 mg/L. TLV was 2-, 4- and 8-fold more potent (MIC90) than daptomycin, vancomycin and linezolid, respectively, when testing SA, and 2-, 8- and 4-fold more potent, respectively, when testing CoNS. Among CoNS, TLV was most active against *S. lugdunensis* (MIC50, 0.06 mg/L) and least active against *S. warneri* (MIC50, 0.25 mg/L; 10 isolates each); MIC50 values for other species (*S. capitis* [20 isolates], *S. epidermidis* [316 isolates], *S. haemolyticus* [34 isolates], and *S. hominis* [59 isolates]) were all 0.12 mg/L. High levels of R to other agents were observed among OX-R SA and CoNS with respective R rates (%) as follows: erythromycin (69.8/68.0), clindamycin (30.0/29.7), gentamicin (19.7/37.9), levofloxacin (90.7/65.7), tetracycline (11.6/18.3) and trimethoprim/sulfamethoxazole (1.9/45.3).

Organism (N)	MIC (mg L)							
	TLV		VAN		LEV		LZD	
	50%	90%	50%	90%	50%	90%	50%	90%
OX-S SA (1556)	0.12	0.12	1	1	⩽0.5	⩽0.5	1	2
OX-R SA (646)	0.12	0.25	1	1	>4	>4	1	2
OX-S CoNS (151)	0.12	0.25	1	2	⩽0.5	⩽0.5	0.5	1
OX-R CoNS (481)	0.12	0.25	2	2	4	>4	1	1

LEV, levofloxacin; LZD, linezolid; TLV, telavancin; VAN, vancomycin.

Conclusions: TLV displayed higher potency than the other agents tested against SA and CoNS (MIC50 and MIC90 values for both, 0.12 and 0.25 mg/L), and inhibited all isolates at ⩽0.5 mg/L. TLV exhibited similar potency for OX-S and -R strains. The continued and rapid emergence of resistant staphylococci, including community-associated OX-R SA, necessitates the timely introduction of new therapeutic agents and longitudinal surveillance to assist in control efforts.

P535 Activity of telavancin against isolates from recently completed Phase 3 studies of complicated skin and skin structure infections

K.M. Krause, S.L. Barriere, M.M. Kitt, B.M. Benton (South San Francisco, US)

Objective: Telavancin (TLV) is a novel, bactericidal lipoglycopeptide with a broad and potent Gram-positive spectrum of activity that includes meticillin-resistant *Staphylococcus aureus* (MRSA). TLV possesses a unique, multifunctional mechanism of action that includes inhibition of cell wall biosynthesis and disruption of bacterial membrane function. The efficacy and safety of TLV have been studied in patients with complicated skin and skin structure infections (cSSSIs) in two methodologically-identical, worldwide, Phase 3 studies (ATLAS 1 and ATLAS 2). Here, we report the susceptibility testing results for TLV and comparators against the Gram-positive isolates collected in these studies.

Methods: A total of 1506 baseline Gram-positive isolates were obtained from 1867 cSSSI patients enrolled in the ATLAS studies throughout North America, Europe, South Africa, South America and Asia during 2005 and 2006. All isolates were identified and susceptibility tests were performed at a central laboratory. MIC values were determined by the CLSI broth microdilution method, using frozen reference MIC panels.

Results: MIC50, MIC90 and ranges for TLV against staphylococci, streptococci and enterococci are shown in the table. Based on MIC90 comparisons, TLV was 2–4-fold more potent than vancomycin, and up to 2-fold more potent than teicoplanin against staphylococci. Teicoplanin was more active against enterococci (MIC90 = 0.25 microg/mL) than TLV or vancomycin (MIC90 = 1 microg/mL and 2 microg/mL, respectively), but less active against coagulase-negative staphylococci (MIC50 = 2 microg/mL). Daptomycin MIC values were similar to TLV against staphylococci and *S. pyogenes*, but were elevated for *S. agalactiae* (MIC90 = 0.25 microg/mL), other *Streptococcus* spp. (MIC90 = 1 microg/mL) and vancomycin-resistant enterococci (MIC90 = 2 microg/mL for *E. faecalis* and MIC50 = 2 microg/mL for *E. faecium*/*E. avium*, respectively). Linezolid MIC90 values were consistently 1–4 microg/mL.

Organism	No. of isolates	TLV MIC (μg/mL)		
		MIC range	MIC_{50}	MIC_{90}
Staphylococcus aureus	1214	0.12–1	0.5	0.5
MSSA	464	0.12–1	0.5	0.5
MRSA	750	0.12–1	0.5	0.5
CoNS	6	0.25–0.5	0.5	NA
Streptococci	201	0.015–0.12	0.06	0.06
S. pyogenes	61	0.015–0.12	0.03	0.06
S. agalactiae	46	0.06–0.12	0.06	0.06
Others*	94	0.015–0.12	0.06	0.06
Enterococci	85	0.06–1	0.5	1
E. faecalis	78	0.25–1	0.5	1
E. faecium and *E. avium*	7	0.06–0.25	0.12	NA

CoNS, coagulase-negative staphylococci; MRSA: meticillin-resistant *S. aureus*; MSSA, meticillin-susceptible *S. aureus*.
*Includes *S. acidominimus*, *S. anginosus*, *S. bovis*, *S. canis*, *S. constellatus*, *S. dysgalactiae*, *S. dysgalactiae ssp. equisimilis*, *S. intermedius*, *S. mitis*, *S. oralis*, *S. pneumoniae* and *viridans* group streptococci.

Conclusions: TLV was active against Gram-positive pathogens common in cSSSIs. Based upon MIC90, TLV was among the most active agents tested. These data highlight the potential therapeutic use of TLV in the treatment of cSSSIs due to Gram-positive pathogens.

P536 Activity of telavancin against complicated skin and skin structure infection isolates according to specimen source

B.M. Benton, S.L. Barriere, M.M. Kitt, K.M. Krause (South San Francisco, US)

Objective: Telavancin (TLV) is a novel, bactericidal lipoglycopeptide with a broad and potent Gram-positive spectrum of activity. TLV's unique, multifunctional mechanism of action includes inhibition of bacterial cell wall biosynthesis and disruption of bacterial membrane function. The efficacy and safety of TLV were studied in patients with complicated skin and skin structure infections (cSSSIs) in two identical, worldwide, Phase 3 studies (ATLAS 1 and ATLAS 2). Here, we report the susceptibility testing results by infection type (major abscess, deep/extensive cellulitis, wound, burn or ulcer) for TLV against the Gram-positive isolates collected in these studies.

Methods: A total of 1506 baseline Gram-positive isolates were obtained from among the 1867 cSSSI patients enrolled in the ATLAS studies throughout North America, Europe, South Africa, South America and Asia during 2005–06. All isolates were identified and susceptibility tests were performed at a central laboratory. MIC values were determined by the CLSI broth microdilution method, using frozen reference MIC panels.

Results: See Table.

Conclusions: TLV was active against Gram-positive pathogens common in cSSSIs, irrespective of the infection site. These data highlight the potential therapeutic use of TLV in the treatment of Gram-positive cSSSIs at a variety of infection sites.