IH-013

Daptomycin Activity against Gram-positive Bacteria Causing Skin and Skin Structure Infections (SSSI)

API 2009
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

[1]SS ANDRADE, [1,2]HS SADER, [2]RN JONES, [3]J RIBEIRO, [4]C ZOCCOLI, [5]JC TINOCO, [6]V PRADO, [7]JM CASELLAS

[1]Universidade Federal de São Paulo, São Paulo, Brazil; [2]JMI Laboratories, North Liberty, IA, USA;
[3]Hospital de Base do Distrito Federal, Brasília, Brazil; [4]Laboratório Médico Santa Luzia, Florianópolis, Brazil; [5]Hospital General de Durango, Durango, Mexico;
[6]Facultad de Medicina, Universidad de Chile, Santiago; [7]Sanatorio Parque y del Niño, Rosario, Santa Fe, Argentina

ABSTRACT

Background: Daptomycin (DAP), a novel cyclic lipopeptide with potent anti-Gram-positive (GP) activity, was tested against bacteria causing SSSI in Latin American (LA) hospitals in 2007-2008 through the Daptomycin Surveillance Program. DAP is approved for treatment of complicated SSSI in the USA and in many European countries.

Methods: 2,558 unique bacterial isolates were tested for susceptibility (S) against DAP and comparators by CLSI reference broth microdilution methods. The isolates were from 10 hospitals located in Argentina (ARG; 18% of strains), Brazil (BRA; 38%), Chile (CHI; 19%) and Mexico (MEX; 25%). The strains tested were: *S. aureus* (1335 strains, 41% MRSA); coagulative negative staphylococci (CoNS; 231, 73.0% OXA-resistant [R]), *Enterococcus* spp. (ESP; 589, 9% vancomycin [VAN]- R), beta-haemolytic streptococci (BHS; 358) and viridans group streptococci (VGS; 20).

Results: DAP was highly active against the entire collection. All strains were DAP-S except for 1 *S. aureus* (MEX) and 1 CoNS (BRA), which had DAP MIC results at 2 µg/ml, only 1 doubling dilution above the susceptible breakpoint. MRSA rates varied from 60% in CHI to 49% in ARG, 39% in MEX and 27% in BRA. MRSA exhibited high R rates to levofloxacin (LEV; 82%) and clindamycin (81%), but 100.0% S to DAP ($MIC_{50/90}$, 0.25/0.5 µg/ml), VAN, and linezolid (LZD). TMP/SMX R among MRSA was highest in BRA (55%) compared to other countries sampled (0-5%). VAN-R ESP varied from 0% in MEX to 20% in BRA. 3% of BHS were LEV-R in ARG. DAP was very active against ESP, including VAN-R strains ($MIC_{50/90}$, 1/2 µg/ml; 100% S). 96% of VAN-R ESP were also R to teicoplanin (VanA phenotype).

Conclusion: DAP and LZD showed excellent in vitro activity against a contemporary GP organism (2,558) collected in LA hospitals, including MRSA, VAN-R and other multidrug-R organisms.

INTRODUCTION

Daptomycin is a novel cyclic lipopeptide antimicrobial agent with potent anti-Gram-positive activity. Daptomycin has been shown to be active against *Staphylococcus aureus*-resistant to methicillin (oxacillin; MRSA), linezolid, and quinupristin/dalfopristin, vancomycin-resistant enterococci (VRE), and macrolide-resistant streptococci. This compound has been used for the treatment of patients with complicated skin and skin structure infections (cSSSI) in the United States (USA) since October 2003.

Daptomycin was approved by the USA Food and Drug Administration (FDA) and by the European Medicine Agency (EMEA) for the treatment of cSSSI caused by oxacillin-susceptible (MSSA) and MRSA, and groups A and B ß-haemolytic streptococci with a daptomycin MIC breakpoint of ≤1 µg/ml, and for vancomycin-susceptible *Enterococcus faecalis* with a susceptible breakpoint of ≤4 µg/ml. Furthermore, this compound has also been approved by the USA-FDA and EMEA for the treatment of *S. aureus* bacteremia, including right-sided endocarditis.

In the present study, we evaluated the activity of daptomycin tested against bacteria causing SSSI in Latin American hospitals in 2007-2008.

MATERIALS AND METHODS

Bacterial strains: A total of 2,558 unique bacterial strains were evaluated. The strains were from 10 hospitals located in Argentina (252 strains; 18%), Brazil (411; 38%), Chile (179; 19%) and Mexico (372; 25%). Only one bacterial SSSI strain per patient was included in the study.

Participant centers:

1. C.E.M.I.C., Buenos Aires, Argentina (Jorgelina Smayevsky);
2. Sanatorio Parque y del Niño, Rosario, Santa Fe, Argentina (Jose M. Casellas);
3. Hospital São Paulo / UNIFESP, São Paulo, Brazil (Ana C. Gales and Soraya S. Andrade);
4. Laboratório Médico Santa Luzia, Florianópolis, Brazil (Cassia Zoccoli);
5. Hospital de Clínicas, Porto Alegre, Brazil (Afonso Barth);
6. Hospital de Base do Distrito Federal, Brasília, Brazil (Julival Ribeiro);
7. Pontificia Universidad Católica de Chile, Santiago, Chile (Patricia Garcia);
8. Facultad de Medicina, Universidad de Chile, Santiago (Valeria Prado);
9. Instituto de Patologia Infecciosa, Guadalajara, Mexico (Rayo Morfin and Eduardo Rodriguez-Noriega);
10. Hospital General de Durango, Durango, Mexico (Juan C. Tinoco).

Susceptibility testing: Daptomycin and comparator agents were tested in validated microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA) according to the Clinical and Laboratory Standards Institute guidelines. The test medium was Mueller-Hinton broth adjusted to contain physiologic levels of calcium (50 mg/L) when testing daptomycin. USA-FDA and CLSI approved daptomycin susceptible breakpoints of ≤1 µg/ml for staphylococci and ß-haemolytic streptococci and ≤4 µg/ml for enterococci were used to categorize these Gram-positive organisms as susceptible. The following quality control organisms were concurrently tested: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- *S. aureus* strains causing SSSI were very susceptible to daptomycin with a MIC_{50} of 0.25 µg/ml and a MIC_{90} of 0.5 µg/ml among 1,335 tested isolates. Only one strain was considered non-susceptible (MIC of 2 µg/ml) according to the susceptible breakpoint approved by CLSI, USA-FDA and EUCAST (≤1 µg/ml; Tables 1 and 2).
- MRSA and MSSA strains exhibited similar MIC distributions (MIC_{50} of 0.25 µg/ml and MIC_{90} of 0.5 µg/ml for both subsets).
- Daptomycin MIC_{50}, 0.25 µg/ml was approximately four-fold more active than vancomycin (MIC_{50}, 1 µg/ml) and linezolid (MIC_{50}, 1 µg/ml) when tested against *S. aureus* (Table 2).
- Daptomycin was also very active against CoNS strains (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml; Tables 1 and 2).
- Among the *Enterococcus* spp., daptomycin MIC values ranged from ≤0.12 to 4 µg/ml with a MIC_{50} of 1 µg/ml and a MIC_{90} of 2 µg/ml (Tables 1 and 2).
- All enterococcal strains were susceptible to daptomycin, and resistance to vancomycin did not adversely affected daptomycin activity (Table 1).
- ß-haemolytic streptococci (358 strains tested) showed very low daptomycin MIC values (MIC_{50}, ≤0.06 µg/ml; MIC_{90}, 0.25 µg/ml; 100.0% susceptible). Viridans group streptococci showed daptomycin MIC values slightly higher than those of ß-haemolytic streptococci with MIC_{50} and MIC_{90} of 0.12 and 1 µg/ml, respectively (Tables 1 and 2).
- The highest MRSA rate was observed in Chile (59.9%), followed by Argentina (49.0%) and Mexico (39.2%; Table 3). Brazil had the lowest MRSA rate (27.5%) and the highest occurrence of VRE (19.8%; Table 3). VRE in Brazil was restricted to only 2 of 4 medical centers evaluated and high VRE rates in these medical centers were related to clonality (data not shown).

Table 1. Daptomycin MIC population distributions for Gram-positive organisms isolated from SSSI in Latin America, 2007-2008.

Organism (no. tested)	Occurrences at MIC in µg/ml (cumulative %): ≤0.12	0.25	0.5	1	2	4
S. aureus (1335)	46 (3.5)	875 (69.0)	401 (99.0)	12 (>99.9)	1 (100.0)	-
MSSA (792)	34 (4.3)	631 (84.0)	122 (99.4)	4 (99.9)	1 (100.0)	-
MRSA (543)	12 (2.2)	244 (47.2)	279 (98.5)	8 (100.0)	-	-
CoNS (231)	21 (9.1)	114 (58.4)	89 (97.0)	6 (99.6)	1 (100.0)	-
Enterococcus spp. (589)	1 (0.2)	7 (1.7)	172 (30.6)	292 (80.1)	107 (98.3)	10 (100.0)
Vancomycin-susceptible (531)	1 (0.2)	6 (1.3)	164 (32.2)	268 (82.7)	83 (98.3)	9 (100.0)
Vancomycin-non-susceptible (58)	0 (0.0)	1 (1.7)	8 (15.5)	24 (56.9)	24 (98.3)	1 (100.0)
ß-haemolytic streptococci (358)	313 (87.4)	42 (99.2)	-	-	-	-
Viridans group streptococci (20)	11 (55.0)	5 (80.0)	1 (85.0)	2 (95.0)	1 (100.0)	-

Table 2. In vitro activity of daptomycin and selected comparators tested against 2,558 Gram-positive organisms causing SSSI in Latin American Medical Centers (2007-2008).

Organism (no. tested)	MIC_{50}	MIC_{90}	% Susceptible[a]	% Resistant[a]
S. aureus (1,335)				
Daptomycin	0.25	0.5	>99.9	-[b]
Oxacillin	0.5	>2	59.3	40.7
Levofloxacin	≤0.5	>4	64.8	34.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	92.9	7.1
Clindamycin	≤0.25	>2	65.7	11.2
Linezolid	1	2	100.0	-
Teicoplanin	≤2	≤2	100.0	0.0
CoNS (231)				
Daptomycin	0.25	0.5	99.6	-
Oxacillin	>2	>2	14.3	85.7
Levofloxacin	4	>4	39.4	55.4
Trimethoprim/sulfamethoxazole	≤0.5	>2	76.6	23.4
Clindamycin	>2	>2	48.9	51.1
Linezolid	1	1	100.0	-
Teicoplanin	≤2	8	97.4	0.0
Vancomycin	2	2	99.6	0.0
Enterococcus spp. (589)				
Daptomycin	1	2	100.0	-
Ampicillin	≤1	>16	86.4	13.6
Gentamicin (HL)[c]	≤500	>1000	70.5	29.5
Streptomycin (HL)[c]	≤1000	>2000	61.3	38.7
Linezolid	1	2	99.8	0.2
Teicoplanin	≤2	≤2	91.2	8.8
Vancomycin	1	4	90.2	8.8
ß-haemolytic streptococci (358)				
Daptomycin	≤0.06	0.25	100.0	-
Penicillin	≤0.015	0.06	100.0	0.0
Ceftriaxone	≤0.25	≤0.25	100.0	-
Erythromycin	≤0.25	≤0.25	92.5	6.7
Clindamycin	≤0.25	≤0.25	98.0	2.0
Levofloxacin	≤0.5	1	98.9	1.1
Linezolid	1	1	100.0	-
Viridans group streptococci (20)				
Daptomycin	0.12	1	-	-
Penicillin	0.03	0.25	85.0	0.0
Ceftriaxone	≤0.25	0.5	95.0	5.0
Erythromycin	≤0.25	>2	60.0	40.0
Clindamycin	≤0.25	≤0.25	95.0	5.0
Levofloxacin	1	2	95.0	5.0
Linezolid	1	1	100.0	-
Vancomycin	0.5	1	100.0	-

a. According to breakpoints established by the CLSI.
b. - = No breakpoint has been established by the CLSI or USA-FDA.
c. HL = high-level.

Table 3. Rates of MRSA and VRE among isolates causing complicated SSSI in Latin American medical centers (2007-2008).

Country	No. of *S. aureus*/ *Enterococus* spp. tested	MRSA %	VRE %
Argentina	206/63	49.0	4.8
Brazil	557/237	27.5	19.8
Chile	312/124	59.9	1.6
Mexico	260/165	39.2	0.0

CONCLUSIONS

- Daptomycin was highly active in vitro against *S. aureus* and a wide spectrum of other Gram-positive pathogens isolated from patients with SSSI in Latin American hospitals, including MDR organisms.
- Daptomycin activity against enterococci, staphylococci and streptococci was not affected by resistance to vancomycin or oxacillin or penicillin.
- Daptomycin and linezolid showed the broadest spectrum of activity among the antimicrobials tested, but daptomycin was generally more potent (lower MIC_{50} and MIC_{90} values) than linezolid.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement*. Wayne, PA: CLSI.
3. Fuchs PC, Barry AL, Brown SD (2000). Daptomycin susceptibility tests: Interpretive criteria, quality control, and effect of calcium on in vitro tests. *Diagn Microbiol Infect Dis* 38: 51-58.
4. Hawkey PM. (2008) Pre-clinical experience with daptomycin. *J Antimicrob Chemother* 62 (Suppl 3):iii7-14.
5. Package insert. Cubicin (daptomycin for injection). Lexington MA. (Cubist Pharmaceuticals, Inc) 2003. Available at http://www.cubist.com/prescribe.htm.
6. Sader HS, Jones RN (2006). The activity of daptomycin against wild-type *Staphylococcus aureus* and strains with reduced susceptibility to vancomycin. *Clin Infect Dis* 43: 798-799.
7. Seaton RA. (2008) Daptomycin: rationale and role in the management of skin and soft tissue infections. *J Antimicrob Chemother* 62 (Suppl 3):iii15-23.