P1334
Paper Poster Session
New agents in clinical development against gram-positive bacteria

Activity of the novel FabI inhibitor Debio 1452 against intracellular forms of susceptible and resistant S. aureus: comparison with linezolid, vancomycin and daptomycin

Frédéric Peyrusson[1], Francoise Van Bambeke[2], Paul Tulkens*[2]

[1]*Université Catholique de Louvain, Louvain Drug Research Institute, Bruxelles, Belgium*

[2]*Université Catholique de Louvain, Louvain Drug Research Institute, Brussels, Belgium*

Background:

Debio 1452 (active moiety of the prodrug Debio 1450 currently in Phase II clinical development for staphylococcal infections) specifically targets staphylococci through inhibition of FabI, a critical enzyme for fatty acid synthesis (Kaplan *et al*., AAC 2012;56:5865-74). Debio 1452 has very low MICs (MIC_{90} 0.008 – 0.015 mg/L) against diverse clinical *S. aureus* isolates (methicillin-susceptible [MSSA] as well as methicillin-resistant [MRSA]). Intracellular forms of *S. aureus* play a major role in the persistence and recurrence of infections. Our aim to assess the intracellular activity of Debio 1452 and compare it with that of other anti-staphylococcal agents against a series of strains with different resistance phenotypes.

Material/methods:

MICs: determined according to CLSI recommendations and interpreted using available EUCAST clinical breakpoints. Intracellular infection of THP-1: bacteria: cell ratio of 4 (1h phagocytosis at 37°C; elimination of non-internalized bacteria with 50mg/L gentamicin [Barcia-Macay *et al* AAC 2006:50:841-51]). Intracellular activity: 30h of incubation with antibiotics with CFU counting and normalization to phagocyte cell protein content using a broad range of extracellular concentrations to obtain full concentration-response curves and determination of pharmacodynamic parameters (E_{max} [maximal relative efficacy] and C_s [static concentration]) based on the Hill equation (sigmoidal function; slope factor=1) fitted to the data by non-linear regression.

Results:

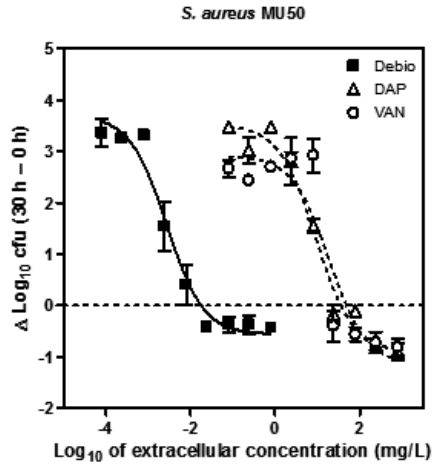
The Table shows MICs and pertinent pharmacodynamic parameters across all strains used, with an illustrative example of full response presented as a figure for MU50. MICs of Debio 1452 were similar for all strains (0.004 mg/L) and unaffected by resistance mechanisms to other drugs. Against intracellular *S. aureus*, the E_{max} of Debio 1452 ranged between -0.4 and -0.7 log CFU, which was similar or slightly lower than that of the other drugs tested. Of interest, Debio 1452 was the most potent drug (lowest C_s value [mg/L]) against resistant strains.

Conclusions:

Debio 1452 is active against intracellular *S. aureus* including strains resistant to other antibiotics. Its intrinsic and intracellular activities remain unaffected by resistance mechanisms affecting the other antibiotics tested, with very low MICs and intracellular static concentrations. These data suggest that Debio 1452 may be useful for controlling infections where intracellular reservoir(s) of susceptible or drug resistant staphylococci may play an important role in the overall pathogenicity of this organism.

Strain	Antibiotic [e]	MIC (mg/L) [f]	E_{max} [g]	C_s [h]	
				mg/L	xMIC
ATCC25923 [a]	Debio 1452	0.004	-0.725	0.008	2.09
	LZD	2	-0.571	12.423	6.211
	VAN	1	-1.075	4.528	4.528
	DAP	1	-0.975	2.609	2.609
MU50 [b]	Debio 1452	0.004	-0.563	0.0181	4.516
	VAN	**8**	-1.145	48.897	6.112
	DAP	**8**	-0.904	36.017	4.502
SA040 LZD^R [c]	Debio 1452	0.004	-0.409	0.027	6.732
	LZD	**16**	-0.692	48.036	3.002
NRS119 [d]	Debio 1452	0.004	-0.556	0.006	1.49
	LZD	**64**	-1.056	683.878	10.686

[a] Laboratory standard (ATCC, Manassas, VA).
[b] ATCC 700699 (Manassas, VA).
[c] Strain from P. Appelbaum, Hershey Medical Center, Hershey, PA; Kosowska-Shick *et al.* (2006) Antimicrob Agents Chemother 50:765–769
[d] NARSA ; Tsiodras *et al* (2001) The Lancet 358: 207 - 208
[e] LZD: linezolid; VAN: vancomycin; DAP: daptomycin
[f] Values in bold characters are above EUCAST susceptibility breakpoints
[g] CFU count decrease (in $\log_{10}$ units) at 30 h from the corresponding initial inoculum as extrapolated from an infinitely high antibiotic concentration; values are means of 2 or 3 independent determinations
[h] Extracellular concentration resulting in no apparent bacterial growth (number of CFU identical to the initial inoculum), as calculated from the Hill equation of the concentration-response curve; values are means of 2 or 3 independent determinations



Concentration-response curves of antibiotics against intracellular *S. aureus* MU50. The graphs show changes in the number of CFU (Δlog CFU from the initial inoculum) per milligram of cell protein in THP-1 cells after 30 h of incubation at increasing extracellular concentrations. The solid horizontal line corresponds to a bacteriostatic effect (no change from the initial inoculum). Data are means ± standard deviations (n = 3); when not visible, error bars are smaller than the symbols.