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Activity of the Peptide Deformylase Inhibitor GSK1322322 against Intracellular Forms of Susceptible and Resistant *S. aureus*: Comparison with Azithromycin, Clindamycin, Linezolid, Vancomycin, Daptomycin, and Moxifloxacin.

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Introduction

- Treatment of staphylococcal infections remains a therapeutic challenge because of the ability of bacteria to survive in intracellular compartments of eukaryotic cells.
- The hydrazinopyrimidine GSK1322322 is a novel antimicrobial agent acting by inhibition of peptide deformylase, an enzyme essential for protein maturation in bacteria [1].
- GSK1322322 is being developed for skin and soft tissue and respiratory tract infections. In this context, the aim of our study was to measure the activity of GSK1322322 against intracellular forms of *S. aureus* in comparison with other currently used anti-staphylococcal antibiotic using strains with different resistance phenotypes.

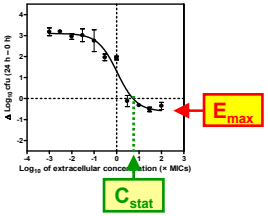
Materials and Methods

Bacterial strains and MIC determinations

- *S. aureus* reference strains ATCC 25923 (MSSA) and resistant strains NRS119, MU50 and N4090440 were obtained as indicated in the Table and grown in MHB as previously described (2).
- MICs were determined according to CLSI recommendations [2] and interpreted using available EUCAST clinical breakpoints [3].

Intracellular activity

- Experiments were performed with human THP-1 cells, displaying macrophage-like activity [4].
- Phagocytosis of opsonised bacteria was allowed for 1h using a 4:1 bacteria-macrophage ratio, followed by elimination of extracellular bacteria by 45 min exposure to gentamicin (50 mg/L).
- Intracellular activity is expressed as the change in the initial inoculum at 24 h compared to the post-phagocytosis value (time 0).
- Data are used to fit a Hill equation allowing to determine key pharmacological descriptors of antibiotic activity:
  - **Emax** : CFU change (in log10 units) at 24h from the post-phagocytosis inoculum as extrapolated for an infinitely large antibiotic concentration
  - **Cstat** : extracellular concentration resulting in no apparent bacterial growth (no. CFU = post-phagocytosis inoculum).



References

1. Sutcliffe JA Ann N Y Acad Sci. 2011;1241:122-52
2. Performance Standards for Antimicrobial Susceptibility Testing; 23d Informational Supplement. CLSI document M100-S23. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
3. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, 2014. http://www.eucast.org.
4. Barcia-Macay *et al*, Antimicrob Agents Chemother 2006; 50:841-51.

Acknowledgments

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Results

Strains and MICs

strain	antibiotic	MIC (mg/L)	EUCAST [a]
ATCC25923	GSK1322322	1	n/a
	azithromycin	1	S
	clindamycin	0.0625	S
	linezolid	2	S
	vancomycin	1	S
	daptomycin	1	S
	moxifloxacin	0.125	S
N4090440 [b]	GSK1322322	0.5	n/a
	azithromycin	> 256	R
	clindamycin	256	R
NRS119 [c]	GSK1322322	1	n/a
	linezolid	64	R
	moxifloxacin	4	R
MU50 [d]	GSK1322322	1	n/a
	azithromycin	> 256	R
	vancomycin	8	R
	daptomycin	8	R
	moxifloxacin	2-4	R

MICs of GSK 1322322 are similar (0.5-1mg/L) for all strains and, for strains resistant to other antibiotics, irrespective of the corresponding phenotypes

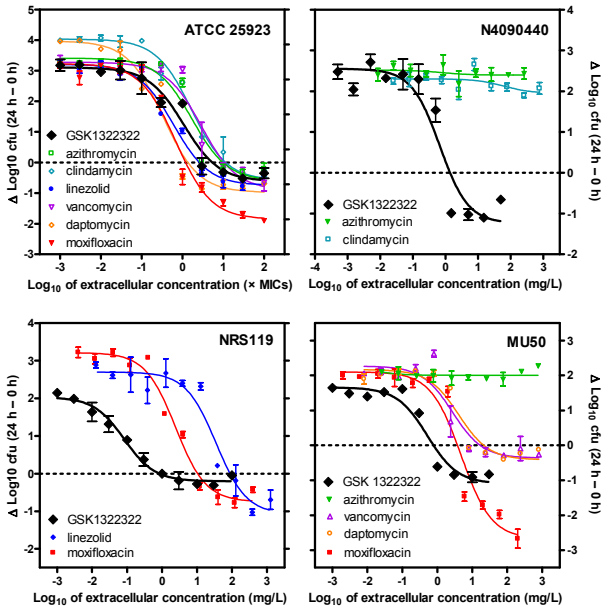
[a] Clinical susceptibility using EUCAST intrepretive criteria [3]
n/a: not available (breakpoints not yet set
S: susceptible (MIC ≤ than the S clinical breakpoint)
R: resistant (MIC > than the R clinical breakpoint)

[b] CHU Mont-Godinne-Dinant (Baudoux *et al.* Journ Antimicrob Chemother 2010;65:1228-1236)

[c] Network on Antimicrobial Resistance in *S. aureus* [NARSA] (Tsiodras *et al.* Lancet 2001;358:207-208)

[d] Network on Antimicrobial Resistance in *S. aureus* [NARSA] (Hiramatsu *et al.* Journ Antimicrob Chemother 1997;40:135-136)

Intracellular activities



GSK 1322322 :

- **shows an *in vitro* intracellular maximal efficacy (E_{max}) similar to all other drugs tested (-0.2 to -1.2 log_{10} CFU) except moxifloxacin (for which E_{max} reaches up to -2.6 log_{10} CFU)**
- **is the most potent drug tested *in vitro* against resistant strains (lowest C_{stat} value, ranging from 0.8 to 4.8 mg/L).**

Conclusions

- GSK1322322 is active against intracellular *S. aureus* including strains resistant to other antibiotics;
- The data suggest that GSK1322322 warrants further study as a potential useful alternative to most currently used anti-staphylococcal agents.