Intracellular Activity of Moxifloxacin (MXF) against European, American, and Asian Clinical Isolates of Community-Acquired Methicillin-Resistant *S. aureus* (CA-MRSA)

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Abstract

Objectives: The chronic and relapsing character of many *S. aureus* infections is often ascribed to bacterial survival in phagocytic cells where commonly recommended antistaphylococcal agents show insufficient bactericidal activity. We showed that MXF is among the most active agents against the intracellular forms of the fully sensitive *S. aureus* strain ATCC 25923 (AAC 2006, 50:841-851), and proves also cidal against an American isolate of CA-MRSA (strain NRS 192; ECCMID 2007, Poster 703). Our objective was to expand these studies to CA-MRSA isolates of more diverse geographical origins.

Methods: MSSA (ATCC 25923) and clinical isolates obtained from North America, East-Asia and continental Europe (as shown in Table; resistance phenotype checked against oxacillin) were tested in parallel for susceptibility in broth (MIC [micro-dilution]) and after phagocytosis by human THP-1 macrophages (24 h change in post-phagocytosis inoculum [delta log CFU] in cells incubated with 4 mg/L moxifloxacin (corresponding to the drug Cmax; see details in AAC 2006; 50:841-851).

Results:

Strains		Geographical origin	Activity in broth (MICs, mg/L)	Intracellular activity (delta log cfu in 24 h)
Resist. phen.	Strain no.			
MSSA	ATCC 25923	USA	0.01-0.03	-2.0 ± 0.1
CA-MRSA	NRS 192	USA[a]	0.03	-1.7 ± 0.1
	NRS 384	USA[a]	0.06	-1.9 ± 0.1
	STA268	TAIWAN[b]	0.03	-1.4 ± 0.1
	DM8064-03	SINGAPORE[c]	0.01	-2.1 ± 0.1
	MEH22256-06	SINGAPORE[c]	0.03	-1.7 ± 0.1
	N4090440	BELGIUM[d]	0.01	-2.1 ± 0.1
	N4042228	BELGIUM[d]	0.03	-2.0 ± 0.0

[a] Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA); [b] Y.C. Huang (Chang Gung Children's Hospital,Taiwan); [c] L. Yang (Singapore General Hospital, Singapore); [d] Y.G. (this study)

Conclusions : MFX shows a constant, close to bactericidal intracellular activity (1.4-2.1 log CFU decrease) against MSSA and all tested CA-MRSA, probably in relation to the low MIC values of the corresponding isolates and irrespective of their geographical origin.

Background

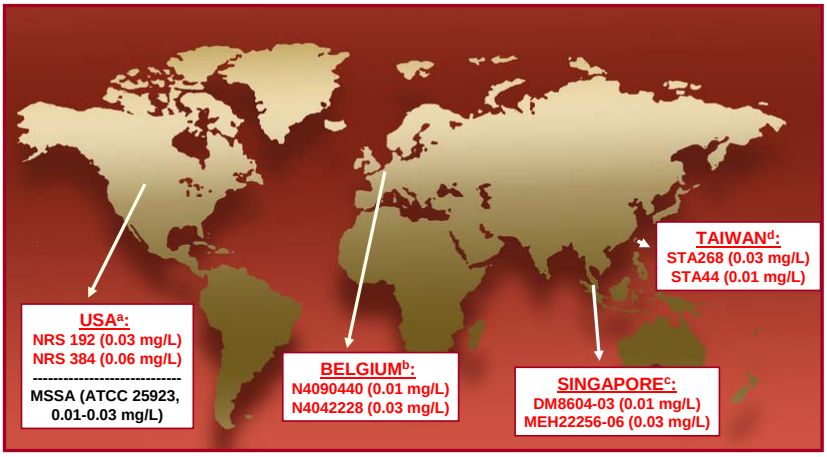
S. aureus is a versatile and aggressive pathogen creating significant public health threat. Intracellular survival of this bacterium is often considered as an important determinant in the persistent and relapsing character of *S. aureus* infections *(Lowy, Trends Microbiol. 2000;8:341-343).* In this context, selecting an optimal treatment to eradicate the intracellular forms of *S. aureus* remains challenging, since routine evaluation of antibiotic activity is only performed against extracellular bacteria. Yet, the intracellular activity of most anti-staphylococcal antibiotics is markedly lower compared to what is observed extracellularly.

We recently showed that moxifloxacin (MXF) is among the most active agents against the intracellular forms of the fully sensitive *S. aureus* strain ATCC 25923 *(Barcia-Macay, Antimicrob Agents Chemother. 2006;50:841-851).* MXF also shows cidal effects against an American isolate of CA-MRSA *(17th ECCMID, 2007, P703).*

We have now measured the intraphagocytic activity of MXF against CA-MRSA from more diverse geographical origins.

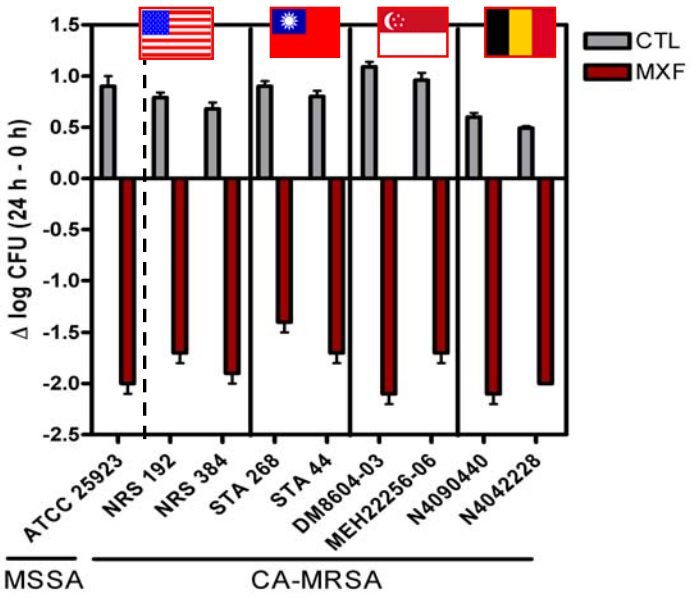
Results

A) Susceptibility testing of MXF towards CA-MRSA



[a] Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA); [b] Y.G. (this study); [c] L. Yang (Singapore General Hospital, Singapore); [d] Y.C. Huang (Chang Gung Children's Hospital,Taiwan);

B) Intracellular activity of MXF



The ordinate shows the change in CFU (log10) per mg of cell protein observed after 24 h of incubations, in comparison with the original inocula, in cells incubated with a concentration of moxifloxacin equivalent to human Cmax (4 mg/L).

Methods

MICs : Susceptibility testing was performed by micro-dilution method in Mueller-Hinton broth according to CLSI guidelines.

Determination of the intracellular antibiotic activity :

(Barcia-Macay, Antimicrob Agents Chemother. 2006;50:841-851)

Cells were infected with preopsonized bacteria (1 h; 37°C), washed with phosphate-buffered saline, and incubated for 45 minutes with gentamicin (50 mg/L) to eliminate non-adherent and non-internalized bacteria. Infected cells were exposed for 24 h to antibiotics at a concentration corresponding to the plasma C_{max} reached in patients treated with conventional dosages (control cells were maintained in the continuous presence of gentamicin [0.5 x MIC] to prevent the extracellular growth of bacteria released from cells).

Conclusions

MXF displays constant and significant intracellular activity against the CA-MRSA isolates tested, disregarding their geographical origin, probably in relation to its low MIC values. Documentation of local MXF susceptibility is warranted.

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