Potential clinical significance of statins on methicillin resistance reversion in *Staphylococcus aureus*

Potencial significado clínico de las estatinas en la reversión de la resistencia a meticilina en Staphylococcus aureus

Dear Editor,

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of hospital-acquired and healthcare-associated infections worldwide.[1] MRSA bacteremia is associated with higher mortality than methicillin-susceptible *S. aureus* bacteremia.[2] For MRSA bacteremia, the IDSA guidelines recommend treatment with vancomycin or daptomycin.[3] However, strains showing higher vancomycin MICs have been associated with increased risk of treatment failure and death,[4] and the emergence of non-susceptible mutants with daptomycin treatment is concerning.[5] In view of these therapeutic difficulties, one possibility is to search for adjuvant substances that allow the continued use of conventional antimicrobials. Some studies have found that statins treatment has a protective effect against both mortality and the development of persistent bacteremia in patients with *S. aureus* bacteremia.[6,7] Statins have no intrinsic bactericidal activity against *S. aureus*,[8] but synergize with different antimicrobials to increase their bactericidal effect.[9] In addition, it has been shown that several statins can reverse methicillin resistance in the community-associated MRSA strain USA300.[8] Despite this phenomenon was confirmed in an experimental murine model,[8] significant questions remain unresolved, and no studies have evaluated the impact of statins as a strategy to reverse methicillin resistance against clinical isolates of MRSA under human therapeutic concentrations. We tested statins against a set of clinical isolates of MRSA belonging to the most prevalent high-risk clones in human infections to address this question.

Nineteen MRSA isolates recovered from patients with nosocomial or healthcare-associated bacteremia were selected for this study. Isolates belonged to the following high-risk clones: ST5 (thirteen isolates), ST8 (four isolates), ST22 (one isolate) and ST45 (one isolate). Thirteen isolates belonged to *agr* group II and the remainder to *agr* group I. All isolates harboured SCC*mec* type IV, and none of the isolates carried Panton-Valentine leukocidin genes.[10] *S. aureus* ATCC 29213 and MRSA USA300 strains were included as controls.

Table 1
Oxacillin MIC of MRSA clinical isolates in the presence of the lactone form of simvastatin.

Strain	Sequence type	*SSCmec* type	*Agr* group	Oxacillin MIC (mg/L)[a]							
				400 μmol/L SIM[b]	200 μmol/L SIM	100 μmol/L SIM	50 μmol/L SIM	25 μmol/L SIM	12.5 μmol/L SIM	6.25 μmol/L SIM	0 μmol/L SIM
ATCC 29213	–	–	–	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
MRSA USA300	ST8	*SSCmec* IV	*agr*I	0.06	0.06	8	16	16	16	16	16
MRSA 14	ST5	*SSCmec* IV	*agr*II	2	4	8	64	64	64	64	64
MRSA 15	ST5	*SSCmec* IV	*agr*II	8	8	64	64	64	64	64	64
MRSA 16	ST5	*SSCmec* IV	*agr*II	2	2	4	8	32	32	32	32
MRSA 17	ST5	*SSCmec* IV	*agr*II	0.06	0.06	16	64	64	64	64	64
MRSA 18	ST5	*SSCmec* IV	*agr*II	0.06	0.06	32	32	32	32	32	32
MRSA 19	ST5	*SSCmec* IV	*agr*II	0.06	0.06	4	16	16	16	16	16
MRSA 20	ST5	*SSCmec* IV	*agr*II	0.06	0.06	8	64	64	64	64	64
MRSA 21	ST5	*SSCmec* IV	*agr*II	0.06	0.06	8	64	64	64	64	64
MRSA 22	ST5	*SSCmec* IV	*agr*II	0.06	0.06	4	32	32	32	32	32
MRSA 23	ST5	*SSCmec* IV	*agr*II	0.06	0.06	32	32	32	32	32	32
MRSA 24	ST5	*SSCmec* IV	*agr*II	0.06	0.06	16	16	16	16	16	16
MRSA 25	ST5	*SSCmec* IV	*agr*II	0.06	0.06	32	64	64	64	64	64
MRSA 26	ST5	*SSCmec* IV	*agr*II	0.06	0.06	16	64	64	64	64	64
MRSA 27	ST8	*SSCmec* IV	*agr*I	0.06	0.06	8	32	32	32	32	32
MRSA 28	ST8	*SSCmec* IV	*agr*I	0.06	0.06	32	32	32	32	32	32
MRSA 29	ST8	*SSCmec* IV	*agr*I	0.06	0.06	16	32	32	32	32	32
MRSA 30	ST8	*SSCmec* IV	*agr*I	0.06	0.06	0,06	64	64	64	64	64
MRSA 32	ST22	*SSCmec* IV	*agr*I	0.06	0.06	16	128	128	128	128	128
MRSA 33	ST45	*SSCmec* IV	*agr*I	0.06	0.06	4	16	32	32	32	32

[a] According to EUCAST breakpoints, *S. aureus* isolates with oxacillin MIC values >2 mg/L are mostly methicillin-resistant due to the presence of the mecA or mecC genes.
[b] SIM: lactone form of simvastatin (inactive form).

The active forms of five statins were tested: fluvastatin, rosuvastatin, atorvastatin, simvastatin and lovastatin (Axxora, Brussels, Belgium). In the case of simvastatin and lovastatin, the prodrug form (lactone) was also included (Axxora). Susceptibility to statins and oxacillin (Sigma-Aldrich, Madrid, Spain) was determined by broth microdilution. All isolates showed MIC values of all statins tested above 200 μmol/L and oxacillin MICs ≥ 16 mg/L (Table 1). Statin–oxacillin synergy was evaluated using the chequerboard method. None of the statins evaluated showed synergistic effects with oxacillin, except for the prodrug form of simvastatin. The lactone form of simvastatin reversed methicillin resistance (defined as the reduction of oxacillin MIC to ≤2 mg/L) in eighteen isolates (95%) at 400 μmol/L, and in seventeen isolates (89%) at 200 μmol/L. However, methicillin resistance reversion was not observed in any isolate at lower concentrations of simvastatin (Table 1). The MIC of the lactone form of simvastatin was >800 μmol/L, which means that this effect is observed at sub-MIC concentrations of simvastatin.

Several studies have shown the pleiotropic effects of statins, including bactericidal activity against gram-positive bacteria, such as *S. pneumoniae*, and reversion of methicillin resistance in *S. aureus*.[8,11] These effects were detected at statin concentrations of 1–100 μmol/L. Nevertheless, the mean concentration of statins in human serum is only 1–15 nmol/L, and the peak concentration is 6–50 nmol/L, with this concentration being reached in serum for a very short period of time.[12]

According to our results, the inactive form of simvastatin is the only statin tested which is able to reverse methicillin resistance in *S. aureus* clinical isolates, although this effect was observed at sub-MIC simvastatin concentrations above 100 μmol/L. Moreover, this concentration of statin is much higher than that reached in serum with therapeutic doses, so that it cannot be used as a potential adjuvant to reverse methicillin resistance. Why this effect is not observed with the prodrug form of simvastatin remains unknown.

These results contrast with those previously found in a murine model of pulmonary infection.[8] This discrepancy might be partially explained by the differences in dosage. In humans, the dosage of statins is approximately 0.1–1 mg/kg, while in the murine model, doses of 20 and 50 mg/kg were used. However, these doses were similar to those used in previous *in vitro* studies.[11] The metabolism, pharmacodynamics and action of statins differ in humans and mice so that the results observed in murine models should be taken with caution before being applied to humans.

This study shows that simvastatin maybe a potential strategy to reverse methicillin resistance in *S. aureus*, although, unfortunately, this effect is not observed at therapeutic human concentrations.

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Conflicts of interest

None to declare.

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