Ceftaroline Activity against *mecC*-Containing *Staphylococcus aureus*

Sushmita D. Lahiri,* Richard A. Alm*

Infection Innovative Medicines Unit, AstraZeneca R&D Boston, Waltham, Massachusetts, USA

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the leading causes of nosocomial infections worldwide, although several different epidemiological lineages are now recognized. A recent emerging lineage of MRSA is livestock-associated methicillin-resistant *S. aureus* (LA-MRSA). First isolated from a bovine milk sample in Great Britain (1), these pathogens have now been isolated from a wide range of animal species in a large number of European and Asian countries (2–4). In addition, there have been several reports of isolates from LA-MRSA lineages causing a variety of severe infections in humans, from skin and skin structure infections to bacteremia (2). The LA-MRSA isolates carry a horizontally acquired SCCmec type XI cassette which encodes an alternative penicillin-binding protein called MecC which has been demonstrated to be sufficient and responsible for mediating resistance to methicillin (5). The cephalosporin ceftaroline fosamil has been approved for the treatment of acute bacterial skin and skin structure infections as well as community-acquired pneumonia. The major area of differentiation from other β -lactam drugs is the activity of ceftaroline (the active metabolite of ceftaroline fosamil) against MRSA, which is the result of improved affinity against the alternative penicillin-binding protein PBP2a (or MecA) that is also horizontally acquired on other SCCmec cassettes. However, substitutions in MecA have been linked to decreased susceptibility to ceftaroline, although those present in the non-penicillin-binding domain (nPBD) have less effect than those in the transpeptidase active site in the penicillin-binding domain (PBD) (6–10). During the genetic characterization of MRSA isolates collected during a 2012 surveillance program, a MRSA isolate (TRN6234) that contained a MecC protein identical to the protein encoded by LA-MRSA isolate LGA251 was identified from a patient in a German hospital with a serious wound infection (1). This *mecC*-containing MRSA isolate, which be-

longed to the ST-130 group, was susceptible to ceftaroline (MIC, 1 μ g/ml) but was resistant, as expected, to other β -lactam drugs (methicillin, 128 μ g/ml; oxacillin, 16 μ g/ml; meropenem, 4 μ g/ml; cefepime, 64 μ g/ml; ceftazidime, >256 μ g/ml).

An alignment demonstrates that MecA from *S. aureus* N315 (GenBank accession number BAB41256) and MecC (GenBank accession number KT192641) share only 63% identity (84% similarity) across the entire protein. However, the penicillin-binding domain (residues 327 to 668) is more highly conserved (75.2% identity and 93.3% similarity) than the non-penicillin-binding (also called the dimerization or allosteric) domain (residues 1 to 326) (50.3% identity and 74.2% similarity), which is likely indicative of the functional importance of the respective domains (Fig. 1). The crystal structure of MecA in complex with ceftaroline has recently been solved (PDB accession number 3ZG0) (11). Analysis of this structure suggests that 19 residues (Gly402, Ser403, Lys406, Tyr446, Glu447, Ser461, Ser462, Asn464, Tyr519, Gly520, Gln521, Thr582, Lys597, Ser598, Gly599, Thr600, Ala601, Glu602, and Ala642) are involved in binding interactions with ceftaroline in

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Address correspondence to Richard A. Alm, ralm@macrolide.com.

* Present address: Sushmita D. Lahiri, Macrolide Pharmaceuticals, Lexington, Massachusetts, USA; Richard A. Alm, Macrolide Pharmaceuticals, Lexington, Massachusetts, USA.

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FIG 1 Alignment of the alternative PBPs, MecA and MecC. The identical residues are boxed, and the MecA (PBP2a) residues that form the ceftaroline binding pocket are shaded gray. The variations in MecA that have been found in MRSA isolates that exhibit a ceftaroline MIC of ≥ 2 μ g/ml (6–10) are shown above the respective MecA protein residues. The GenBank accession numbers for MecA (strain N315) and MecC (strain TRN6234) are BAB41256 and KT192641, respectively.

the transpeptidase pocket. A total of 17 of these are conserved in MecC (Fig. 1). Significantly, the binding pocket variation most commonly observed in ceftaroline-resistant MRSA isolates, E₄₄₇K, is already present in MecC. The only other difference is the relatively conservative hydrophobic Y₄₄₆F substitution. In MecA, this Y446 residue has been implicated in high-level resistance to ceftaroline, albeit as a polar Y₄₄₆N substitution (8). This suggests that despite the high level of identity between the PBDs of these two alternative penicillin-binding proteins, subtle conformational differences which impact the binding mode of ceftaroline likely exist, and we await a cocomplex structure to interpret the differences. Furthermore, several of the residues in the nPBD that are often altered in MRSA isolates that have slightly decreased susceptibility to ceftaroline (MIC, 2 µg/ml) are also not conserved in MecC (6, 8, 9). These include E239 and N146. These residues are located in a region of MecA that has been proposed to be functionally important during cell wall biosynthesis, by interaction either with other PBPs (6) or with other ligands, such as cell wall fragments, that may regulate the transpeptidase pocket activity allosterically (11), suggestive of additional subtle differences between the two alternative PBPs. Indeed, the E₂₃₉K/E₄₄₇K MecA combination has been observed in ceftaroline-resistant MRSA isolates (MIC, 8 µg/ml) (6, 10), and yet the same changes in MecC left isolates susceptible to ceftaroline.

In summary, although the activity of ceftaroline needs to be tested against additional *mecC*-containing isolates with characteristics similar to those of the LA-MRSA lineages, these initial data against this MecC-containing isolate suggest that ceftaroline fosamil may represent a possible therapeutic alternative for this emerging zoonotic pathogenic lineage of MRSA.

Nucleotide sequence accession number. Sequences were deposited in GenBank under accession number [KT192641](#).

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