Abstract (updated)

Staphylococcus aureus remains a therapeutic challenge, due in part to the ability of this organism to acquire resistance mechanisms to most recommended antibiotics [1] and to survive in intracellular compartments of eukaryotic cells [2]. In this context, it is therefore essential (i) to foster the discovery and development of novel antibiotics with modes of action distinct from those currently in use, and (ii) to assess the activity of these molecules against intracellular S. aureus.

Methods

Gepotidacin (formerly GSK2140944 - see hereunder) is an antistaphylococcal antibiotic. Gepotidacin demonstrates extracellular and intracellular activity similar to or better (more negative Emax) than some of the most recommended antibiotics, including fluoroquinolones. Gepotidacin is presently in clinical development.

The aim of our study was to assess and measure the activity of Gepotidacin against extra- and intracellular forms of S. aureus, compared to other commonly used antimicrobial agents. This study was conducted with different lineages of susceptible and resistant strains of S. aureus: Sa1 (CLSI susceptible strain, ATCC25923), Sa2 (CLSI resistant strain, ATCC700699), Sa3 (CLSI susceptible strain, ATCC35767) and Sa4 (CLSI resistant strain, ATCC35767).

Results

Gepotidacin: MICs ranged from 0.25–1 mg/L for all strains and were unaffected by resistance mechanisms to other antibiotics, including efflux by the ciprofloxacin efflux transporter AcrA.

Discussion and Conclusions

Gepotidacin shows extracellular and intracellular activities that remain unaffected by resistance mechanisms to other antibiotic classes.

While its intracellular maximal efficacy (Emax) is considerably lower than its extracellular activity (as for all other antibiotics), the intracellular relative potency (C50) of gepotidacin is close to its MICs in broth, suggesting a free penetration and an effective antibacterial activity against intracellular S. aureus.

Gepotidacin demonstrates extracellular and intracellular activity similar to or better (more negative Emax) than that of daptomycin, linezolid and clarithromycin.

These data suggest that gepotidacin may warrant further study as a potential anti-staphylococcal agent against intracellular multidrug resistant S. aureus.