Delafloxacin Activity against Staphylococcus aureus with Reduced Susceptibility or Resistance to Methicillin, Vancomycin, Daptomycin or Linezolid

Introduction

- Delafloxacin (ABT 492) is a new fluoroquinolone that is available in both oral and parenteral formulations.
- Delafloxacin has been approved by the Food and Drug Administration (FDA) for the management of acute bacterial skin and skin structure infections.
- Delafloxacin's in vitro activity and favorable clinical response against MRSA infections distinguishes it from other fluoroquinolones.
- This research focused on evaluating delafloxacin's activity against MRSA strains including blood isolates and isolates with reduced susceptibility or resistance to daptomycin, vancomycin, linezolid, and levofloxacin.
- We also evaluated activity based upon SCC mer typing.

Materials

- A collection of 183 isolates were selected for in vitro testing:
  - Vancomycin-resistant S. aureus (VRSA) (n=15), vancomycin intermediate S. aureus (VISA) (n=31), linezolid resistant S. aureus (LISA) (n=4) and, heteroresistant VISA (hVISA) (n=1), were obtained from the Network on Antimicrobial Resistance in Staphylococcus aureus (NARS) program (now known as BEI Resources).
  - Two LISA isolates were obtained from Robson Memorial Medical Center in Ohio. The remaining isolates were samples from Ascension-St. John Hospital.

Methods

- The minimal inhibitory concentration (MIC) of delafloxacin (DFX), levofloxacin (LEV), vancomycin (VAN), daptomycin (DAP), ceftaroline (CFT) and linezolid (LZD) were determined by broth microdilution testing using calcium-adjusted Mueller Hinton broth.
- All testing was performed per CLSI guidelines and all plates were prepared in house. All plates were inoculated with approximately 5 x 10^4 CFU/ml of each isolate and incubated at 35°C for 18 to 24 hours.
- S. aureus ATCC 29213 was used to monitor quality control for all the agents. MICs were read visually as the lowest drug concentration with no visible bacterial growth.
- FDA breakpoints were used to determine delafloxacin susceptibility and CLSI breakpoints were used to determine susceptibility for all the other agents.
- Minimal bactericidal concentrations (MBCs) were also determined, following CLSI guidelines. All testing was performed in triplicate.
- Staphylococcal cassette chromosome mec element (SCC) types were determined by a multiplex PCR method (Zhang et al. 2005, JCM43:5026-5033). Isolates that were non-typeable with the multiplex PCR were analyzed by typing.

Results

- Table 1: MRSA results of blood isolates (n=110) collected at Ascension St. John Hospital
- Table 2a: MIC results of blood isolates (n=64) identified as SCC type IVa
- Table 2b: MIC results of blood isolates (n=16) identified as SCC type IVb
- Table 2c: MIC results of blood isolates (n=15) identified as Vancomycin Intermediate
- Table 2d: MIC results of blood isolates (n=40) identified as Vancomycin Non-susceptible
- Table 3: Delafloxacin results from 55 (of 110) isolates tested with a levofloxacin MIC of ≥ 8.0 mcg/ml
- Table 4a: MIC results of blood isolates (n=30) identified as SCC type IV
- Table 4b: MIC results of blood isolates (n=16) identified as SCC type IVb
- Table 4c: MIC results of blood isolates (n=15) identified as Vancomycin Intermediate
- Table 4d: MIC results of blood isolates (n=15) identified as Vancomycin Intermediate

Conclusions

- Among SCC IVa strains delafloxacin demonstrated a high level of susceptibility (94%) compared to levofloxacin (44%). Both delafloxacin and levofloxacin demonstrated poor activity against the genotype SCC II with 3% and 0% susceptibility, respectively. Since the genotype SCC IVa is most often community-acquired one should anticipate that delafloxacin will be more active against Staphylococcus aureus arising in the community than in the hospital.
- Delafloxacin demonstrated some activity against DNSSA and VISA at 38% and 40% respectively. Delafloxacin is generally not active against VRSA and LISA.
- When evaluating delafloxacin against isolates with levofloxacin MIC’s ≥ 8 mcg/ml suggesting the presence of quinolone resistance-determining regions, delafloxacin was active against 36.4% of strains.
- In vitro activity for delafloxacin will vary based upon resistance to other antimicrobial agents and genetic markers including the number of quinolone resistance-determining region mutations, thus restating the need for performance of susceptibility testing to assist in clinical decision making.

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