Determination of Quality Control Guidelines for MIC Dilation and Disk Diffusion Methods (NCCLS) When Testing LBM415, a Novel Peptide Deformylase Inhibitor

TR FRITSCHEN, TR ANDEREGG, RN JONES
The JONES Group / IMI Laboratories, North Liberty, IA

P923
ECM 2004

ABSTRACT

Background: Quality control (QC) guidelines remain necessary for accurate determination of antimicrobial susceptibility testing and should be established early in the development of new antimicrobial classes. LBM415 is a peptide deformylase (PDF) inhibitor rapidly progressing into Phase II and III human clinical trials, thus QC guidelines appear necessary for NCCLS methods. Methods: Multilaboratory (7 or 8 sites) trials were initiated using the NCCLS M2-A2 guideline for QC determinations. Key technical details were: MIC phase - 4 Mueller-Hinton (MH) broth lots, 8 participant sites and 10 replicates of 4 appropriate QC strains; and disk diffusion phase - 3 Muller-Hinton plates, 7 sites and 10 replicates of 3 appropriate QC strains. Results were analyzed by statistical methods found in M2-A2. Control drugs included vancomycin, chloramphenicol, linezolid and levofloxacin. 99.9 - 100.0% of control results were within published NCCLS ranges (640 and 1050 results for MIC and zone tests, respectively). Inoculum concentration controls averaged 3.3 ± 2.0 (MIC trial only). Results: Seven of the 8 participating sites qualified for results in the 2 separate QC studies, and the calculated (predicted) zone diameter ranges were very close to the expected ranges for S. aureus ATCC 29212 (2.8-4.5 mm; 99.4), S. epidermidis ATCC 51292 (1.5-3.5 mm; 99.4), S. pneumoniae ATCC 6538 (2.5-5.0 mm; 99.4), S. pyogenes ATCC 19433 (12-26 mm; 99.4), S. dysgalactiae subsp. equisimilis ATCC 39320 (6.5-16 mm; 99.4), S. agalactiae ATCC 29,693 (12-20 mm; 99.4), S. aureus ATCC 43328 (20-30 mm; 99.4), S. aureus ATCC 29,247 (25-35 mm; 99.4), S. aureus ATCC 25923 (25-35 mm; 99.4), H. influenzae ATCC 49247 (11-21 mm; 99.4) and H. influenzae ATCC 25923 (30-40 mm; 99.4). All QC ranges were determined to contain ≥ 95% of all reported results.

RESULTS

MIC QC RANGES

- LBM415 MIC distributions when testing S. pneumoniae ATCC 49619 are shown in Table 1. The proposed MIC range was 0.25-4 mg/L, encompassing 97.5% of all reported results.
- Similar results were obtained for S. aureus ATCC 49407 with nearly 60% of all QC results at the midvalue of 2 mg/L. The proposed MIC range was 1-4 mg/L containing ≥ 97.5% of all reported results.
- The results for S. sanguinis ATCC 90023 showed a modal value at 1 mg/L (71.9%) of all reported results and a proposed MIC range of 0.5-2 mg/L that would include ≥ 94% of all results. The range for S. sanguinis ATCC 29,247 had the highest percent of the total results (89.7%) at the MIC modal value of 4 mg/L. The proposed MIC range was 2-8 mg/L.
- The proposed MIC range for the 4 QC strains tested are summarized in Table 2. The proposed log disk dilution ranges for LBM415 broth microdilution tests included 95.6-99.4% of all reported results in this initial study.

DISK DIFFUSION QC RANGES

- LBM415 zone diameter distributions among the 7 participating laboratories when testing S. aureus ATCC 49407 with only 16.9% of the total results at the overall modal value (30 mm), the proposed zone range (25-35 mm) was 11-18 mm. The overall modal value for S. pneumoniae ATCC 49619 was 33 mm (32.1% of total results). The proposed QC range (24-34 mm) was calculated from the median (33 ± 3 mm) as determined by NCCLS calculations plus an additional 1 mm at the upper 95% of the range to achieve ≥ 95% of results.
- The overall modal value for H. influenzae ATCC 49247 was 28 mm (21.2% of total results). The proposed QC range (22-32 mm) was calculated from the median method and included 99.8% of all of the laboratory results.
- All 4 QC strains exhibited similar values among participating laboratories, thus indicating some difficulty in reading zone diameter results. Three different authors of zone diameter ranges for LBM415 on 3 different media lots were compared. No significant lot-to-lot variation was observed.
- The proposed zone diameter ranges for the 3 QC strains are summarized in Table 4. The overall modal value for S. pneumoniae ATCC 49628, 12 mm range for S. aureus ATCC 25923 and 9 mm range for H. influenzae ATCC 49247 included 97.6-99.8% of reported disk diffusion zone diameter results.

CONCLUSIONS

- This study summarizes results from a NCCLS M2-A3 study design to establish LBM415 broth microdilution MIC and zone diameter QC ranges.
- While guidelines for antimicrobial resistance in clinically significant organisms are necessary, the goal now for new antimicrobial agents with novel target sites of action becomes increasingly important. LBM415, a novel clinical candidate PDF inhibitor, has demonstrated excellent in vitro activity against the gram-positive and -negative organisms most frequently recovered from respiratory tract and skin and soft-tissue infections.

SELECTED REFERENCES