The authors’ conclusion that ceftolozane-tazobactam plus metronidazole was “noninferior” in efficacy to meropenem for treatment of cIAI was strictly true, based on the prespecified margin of noninferiority [1]. However, a curiosity of noninferiority trials is that achieving statistical noninferiority does not mean that the drug is actually not inferior in efficacy. In fact, the point estimate for the difference in the primary endpoint (clinical cure) in the microbiological intention to treat (MITT) population was −4.2 with a 95% confidence interval (CI) heavily imbalanced in favor of meropenem, which only narrowly crossed 0 (−8.9% to +0.5%). Although these results meet the predefined criterion for noninferiority, they also strongly suggest that ceftolozane-tazobactam/metronidazole may be inferior in efficacy to meropenem for treating cIAI. Indeed a Fisher exact test run on the reported data yields a \( P \) value of .054, indicating near statistical confirmation of meropenem superiority. Evaluating the failure rates in each arm underscores this point: 17.0% for ceftolozane-tazobactam/metronidazole vs 12.7% for meropenem, a 33.8% relative increase in clinical failure.

In addition to the mortality rates in the current study (2.3% ceftolozane-tazobactam vs 1.6% meropenem), the package insert for the drug reports that across cIAI phase 2 and 3 trials, “death occurred in 2.5% (14/564) of patients receiving ZERBAXA and in 1.5% (8/536) of patients receiving meropenem,” also raising concerns that ceftolozane-tazobactam may be clinically inferior to meropenem [2]. Yet the US Food and Drug Administration (FDA) approved ceftolozane-tazobactam for a cIAI indication based on the statistical noninferiority criterion.

Also concerning is the fact that the large majority of patients enrolled were in Eastern Europe, where patient populations and care standards do not clearly extrapolate to conditions in the United States. Furthermore, in the Eastern European microbiologically evaluable cohorts, the treatment success rates were extremely high at 96% to 97%. Even in the MITT population, success rates exceeded the expected 75% rate used to plan for the study’s power and sample size, as well as historical success rates in cIAI trials (FDA’s meta-analysis revealed an 81.7% [95% CI, 78.9%–84.4%] historical success rate) [3]. Such high success rates may indicate a patient population that is not nonrepresentative of cIAI patients requiring intensive antibiotic therapy in the US, and will tend to bias the trial results towards achieving noninferiority. Despite this, the overall study results clearly trend to inferiority of the experimental regimen.

Although ceftolozane-tazobactam had impressive efficacy in its cUTI trial [4], its relative efficacy for treating cIAI is concerning. Clinicians may encounter individual patients with cIAI caused by organisms with resistance profiles requiring ceftolozane-tazobactam therapy. However, they should recognize that routine use of this regimen in preference to meropenem risks an increased failure rate for cIAI overall.

Note

Potential conflict of interest. In the last year, B. S. has received grants/contract support from Dipexium, consulting fees from Glaxo SmithKline, Cempra, PTC Therapeutics, The Medicines Company, and Medimmune, and owns equity in Motif, Synthetic Biologics, and BioAIM. E. P. B. has been a consultant to Cerexa, Sanofi, Hospira, Therametrics, Celltrion, Acerta Pharma, Kythera Biopharmaceuticals, Clarus Therapeutics, Trius Therapeutics, Takeda, NPS Pharmaceuticals, Merck, Amgen, Bayer, Catabasis, 3D Communications, Novo Nordisk, McNeil, Novartis, GlaxoSmithKline, Consumer Healthcare Products Association, and has equity in Catabasis and Calistoga Pharmaceuticals. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Brad Spellberg\(^1\) and Eric P. Brass\(^2\)

\(^1\)Los Angeles County+University of Southern California (LAC+USC) Medical Center, and \(^2\)Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California

References


Noninferiority Doesn’t Mean Not Inferior

To the Editor—We have several concerns about the study comparing ceftolozane-tazobactam plus metronidazole to meropenem for the treatment of complicated intra-abdominal infection (cIAI) [1]. These concerns illustrate some of the challenges in conducting and interpreting noninferiority trials.