CLINICAL INVESTIGATION

Non-inferiority designs and novel antimicrobials

Keywords: ceftolozane/tazobactam • CRE • ESBL • intra-abdominal infections • multidrug-resistant

Giorgio Tarchini*
Cleveland Clinic Florida 2950 Cleveland Clinic Blvd Weston, FL 33331, USA
*Author for correspondence:
Tel.: +1 954 659 5165
Fax: +1 954 659 5166
tarchig@ccf.org

Joseph S Solomkin
Joseph S. Solomkin, MD University of Cincinnati Health 222 Piedmont Ave Suite 7000 Cincinnati, OH 45219, USA

The Problem of increasing antimicrobial resistance in Gram-negative organisms

The spread of antimicrobial resistance, particularly among facultative Gram-negative isolates, is now a dominant theme for physicians, drug developers, and regulatory bodies [1] . However, a rational path to approval is not obvious for agents with increased activity against isolates that, while increasing in prevalence, are not the most common causes of community-acquired Gram-negative infections in the USA. These isolates include extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae, carbapenem resistant Enterobacteriaceae and multidrug-resistant (MDR) *Pseudomonas aeruginosa*.

Recent changes in the US FDA approval process

Some have advocated that organism-specific trial designs should be used to study agents with *in vitro* activity against these types of isolates, as either companions or replacements for the historic indication-based clinical trial design [2]. The argument in favor of continuing with indication-based trials is that the characteristics of anatomically different infections (e.g., urinary tract infection [UTI] and complicated intra-abdominal infection [cIAI]) are substantially variant that it is important to understand efficacy in specific sites of infection. Critical variations that may well affect antimicrobial activity include the densities of organisms, interactions of polymicrobial versus monomicrobial infecting flora, and anatomic elements affecting clearance of infecting isolates, and patterns of failure (recurrent systemic signs of infection [UTI] vs surgical site infection [cIAI]). An agent with high penetration into the urine may work well against organisms with higher minimum inhibitory concentrations in UTI, but fail because of penetration problems for intra-abdominal or pulmonary infections. Recent guidance from the FDA allows greater flexibility for regulatory approval [3]. This guidance in effect reduces the number of studies needed for regulatory approval and, therefore, may accelerate availability of potentially novel agents. In the case of ceftolozane/tazobactam, a single UTI study was the necessary companion allowing only one cIAI study to be performed.

Ceftolozane/tazobactam

This discussion has been brought into better focus by the completion of the trial of ceftolozane/tazobactam (plus metronidazole) versus meropenem (plus placebo) for complicated intra-abdominal infection. Ceftolozane is a novel cephalosporin that has demonstrated more potent *in vitro* activity against *P. aeruginosa* compared with the currently available cephalosporins [4]. It is combined with tazobactam, a well-established β-lactamase inhibitor to broaden coverage to include most ESBL-producing *Escherichia coli, Klebsiella pneumoniae*, and other Enterobacteriaceae. Metronidazole was used as an adjunct antibiotic in the study due to the relatively poor activity of ceftolozane/tazobactam against *Bacteroides fragilis* [4]. Ceftolozane/tazobactam is also being developed for the potential

FUTURE SCIENCE part of fsg

treatment of hospital-acquired bacterial pneumonia, a term that includes ventilator-associated pneumonia, at a dose of 3 g every 8 h. Ceftolozane/tazobactam has been granted Fast Track status by the FDA pursuant to the Generating Antibiotics Incentives Now Act for its respective Qualified Infectious Disease Product indications.[5] The Qualified Infectious Disease Product designation allows for certain incentives related to the development of new antibiotics, including eligibility for Fast Track status and Priority Review. Other agents that have received this include ceftazidime/avibactam [6]. All of these regulatory tools are intended to bring agents like ceftolozane/tazobactam to clinical practice more rapidly.

Top line results for the Phase III trial of ceftolozane/tazobactam in complicated intra-abdominal infections have recently been made public [7]. The two trials previously needed for regulatory approval were begun prior to the release of the recent guidance. The program was altered to allow the reduction in total sample size per indication by combining the results from the two protocols in support of a single-study approval pathway for cIAI.

The trial compared ceftolozane/tazobactam, administered intravenously (1.5 g every 8 h [q8h]) plus metronidazole (0.5 g q8h), to meropenem, administered intravenously (1 g q8h), in adult patients with cIAI. A total of 993 patients were enrolled. The trial was designed to demonstrate noninferiority of ceftolozane/tazobactam and metronidazole to the comparator meropenem and met the FDA and the European Medicines Agency defined primary end points of statistical noninferiority compared with meropenem. In the microbiologically evaluable population suffering from infections caused by Gram-negative aerobic pathogens microbiological eradication rates of 234/243 (96.3%) and 269/282 (95.4%) were seen in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively. These are historically high rates for success compared with data from previous trials [8].

The presumed or confirmed microbiological eradication rates were 193/201 (96.0%) versus 214/225 (95.1%) for *E. coli* and 28/28 (100%) versus 22/25 (88.0%) for *Klebsiella pneumoniae* for the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively. All infections with *P. aeruginosa* were eradicated in both treatment groups, 25/25 (100%) in the ceftolozane/tazobactam plus metronidazole arm and 28/28 (100%) in the meropenem arm. Overall, a total of 58 subjects in the modified intention to treat population had baseline intra-abdominal pathogens that were confirmed to be ESBL-positive, including 29 subjects in each arm (7.5 vs 7.0% of subjects in the ceftolozane/tazobactam plus metronidazole vs meropenem treatment arms, respectively). In the microbiologically evaluable population, 100% (22/22) of subjects in the ceftolozane/tazobactam plus metronidazole treatment arm were clinical cures compared with 88.5% (23/26) of subjects in the meropenem treatment arm, demonstrating a therapeutic effect of ceftolozane/tazobactam for ESBL-producing Enterobacteriaceae.

Optimal design of Phase III clinical trials of new antibiotics for complicated intra-abdominal infections

Are these numbers sufficient to document efficacy against the specific target pathogens? Certainly, the high cure rates seen in both arms of this trial, higher than seen in previous clinical trials using meropenem [8], raise concerns regarding the discriminatory power of this particular trial. There have been other advances in the management of cIAI, particularly including both percutaneous and laparoscopic intervention, and these may account for improved outcomes. We await the final study report to examine this point. The distribution of APACHE severity scores in this trial compared with others will also be of interest.

Given the inclusion and exclusion criteria commonly used for cIAI trials, effectively prohibiting entry of patients who have received prior antibiotic therapy, indication-based trials are not efficient means of collecting outcomes of MDR isolates. In the current trial, for example, few, if any, MDR-*Pseudomonas* were isolated. Determining the clinical efficacy of ceftolozane/tazobactam against this highly resistant organism is of particular importance due to its potentially useful role in treating pseudomonal infections caused by carbapenem-resistant strains in multiple settings, including ventilator-associated pneumonia. Ceftolozane/tazobactam is a promising agent, however, development of agents also active against carbapenem resistant Enterobacteriaceae remains a major priority.

Currently, we depend on anedoctal evidence from observational trials for data on the efficacy of antimicrobials against highly resistant pathogens [9–12]. Observational trials are plagued by strong potential bias stemming from the lack of control the investigator can exert on the situation being observed. As a result, it is arduous to ensure that a cause-and-effect relationship truly exists. This could lead to either overestimating or underestimating the effect of a particular antibiotic against specific MDR organisms.

It is in light of the above that we underscore the synergistic benefits of indication- and organism-specific trials designed to specifically answer this type of questions. Such trials could also provide more robust

data regarding efficacy against ESBL producing Enterobacteriaceae.

Financial & competing interests disclosure

JS Solomkin is a consultant for Cubist, AstraZeneca,Tetraphase, Theravance and Amicrobe, and has given lectures supported by Merck, Bayer and Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

References

1 Munoz-Price LS, Poirel L, Bonomo RA *et al.* Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. *Lancet Infect. Dis.* 13, 785–796 (2013).

2 Infectious Diseases Society of America. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. *Clin. Infect. Dis.* 55, 1031–1046 (2012).

3 Guidance for Industry: complicated intra-abdominal infections: developing drugs for treatment. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321390.pdf

4 Sader HS, Rhomberg PR, Farrell DJ *et al.* Antimicrobial activity of CXA-101, a novel cephalosporin tested in combination with tazobactam against *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* strains having various resistance phenotypes. *Antimicrob. Agents Chemother.* 55, 2390–2394 (2011).

5 Establishing a list of qualifying pathogens under the FDA safety and innovation act. www.federalregister.gov/articles/2013/06/12/2013–13865/establishing-a-list-of-qualifying-pathogens-under-the-food-and-drug-administration-safety-and

6 Forest Laboratories' ceftazidime/avibactam gets QIDP designation from US FDA. http://drugdiscovery.pharmaceutical-business-review.com/news/forest-laboratories-ceftazidimeavibactam-gets-qidp-designation-from-us-fda-130913

7 Cubist's investigational antibiotic ceftolozane/tazobactam meets endpoint in Phase III study. www.drugdevelopment-technology.com/news/newscubist-reports-encouraging-phase-iii-trial-results-of-ceftolozanetazobactam-to-treat-ciai-4147430

8 Lucasti C, Jasovich A, Umeh O *et al.* Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a Phase III, prospective, multicenter, randomized, double-blind, noninferiority study. *Clin. Ther.* 30(5), 868–883 (2008).

9 Birmingham MC, Rayner CR, Meagher AK *et al.* Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. *Clin. Infect. Dis.* 36(2), 159–168 (2003).

10 Linden PK, Kusne S, Coley K *et al.* Use of Parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. *Clin. Infect. Dis.* 37, e154–e160 (2003).

11 Anthony KB, Fishman NO, Linkin DR *et al.* Clinical and microbiological outcomes of serious infections with multidrug-resistant Gram-negative organisms treated with tigecycline. *Clin. Infect. Dis.* 46, 567–570 (2008).

12 Eckmann C, Heizmann WR, Leitner E *et al.* Prospective, non-interventional, multi-centre trial of tigecycline in the treatment of severely ill patients with complicated infections – new insights into clinical results and treatment practice. *Chemotherapy* 57, 275–284 (2011).