New Antimicrobial Agents

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ABSTRACT

Infections caused by resistant pathogens are increasing and are a major threat to patient outcomes. A 2013 US Centers for Disease and Control and Prevention report on antibiotic resistance threats indicates that 2 million Americans acquire antibiotic-resistant infections annually and at least 23,000 die. Increasing resistance of bacterial pathogens to virtually all available antimicrobial classes signals the emergent need for new agents. Only 12 antibiotics were approved by the US Food and Drug Administration between 2000 and 2012. Initiatives to increase the number of effective antibiotics have been enacted. This study addresses the mechanism of action, microbiology, indications, dose, safety, drug interactions, and place in therapy of dalbavancin, tedizolid, oritavancin, ceftolozane/tazobactam, and ceftazidime/avibactam.

Keywords: ceftazidime/avibactam, ceftolozane/tazobactam, dalbavancin, oritavancin, tedizolid

INTRODUCTION

Despite increasing resistance among both Gram-positive and Gram-negative bacteria, antimicrobial agent development over the last 20 years has slowed dramatically—since 2000, only 12 antimicrobial agents have been approved. The increase in antibiotic-resistant pathogens has resulted in dwindling numbers of efficacious antimicrobial agents available to treat patients with resistant pathogens. According to the United States Centers for Disease Control (CDC) report, *Antibiotic Resistance Threats in the United States, 2013*, 2 million individuals acquire antibiotic-resistant infections each year and at least 23,000 of these patients die as a result. The CDC report states that developing new antibiotics is one of the four core actions needed to help fight resistant bacteria.[1]

Developing new antimicrobial agents is a challenging, timely, and costly process. The number of pharmaceutical companies involved in antibiotic research has decreased significantly. With regard to drug development, approximately 1 in 5 agents that reach the initial phase of testing receive approval from the US Food and Drug Administration (FDA).[2] This is coupled with the fact that antibiotics are only used for a short period of time as compared with agents used for the management of chronic diseases (ie, hypertension). In 2010, the Infectious Diseases Society of America proposed the 10 × '20 Initiative, in support of the development of 10 new systemic antimicrobial agents by 2020.[3] To address these concerns, The US Congress enacted the Generating Antibiotic Incentives Now Act, under the FDA's Safety and Innovation Act. The Generating Antibiotic Incentives Now Act provides drug manufacturers with an additional 5 years of exclusivity for qualifying new antimicrobial agents. The qualifying agents are referred to as a Qualified Infectious Disease Product and are defined as those antimicrobial agents that are intended to treat serious or life-threatening infections, including resistant pathogens (as defined by the FDA). These agents are eligible for priority review and fast track status. In 2015, President Obama proposed that the 2016 budget would include $1.2 billion for combating resistant infections.[4]

Since 2010, the FDA has approved 6 new systemic antimicrobial agents. These include ceftaroline, dalbavancin, tedizolid, oritavancin, ceftolozane/tazobactam, and ceftazidime/avibactam. Five of these agents were granted priority review and approval as a Qualified Infectious Disease Product—dalbavancin, tedizolid, oritavancin, ceftolozane/tazobactam, and ceftazidime/avibactam. This article addresses the mechanism of action, clinical microbiology,

indications, dose/administration/cost, adverse effects, drug interactions, and place in therapy for the agents approved in 2014 and the first half of 2015.

CEFTOLOZANE/TAZOBACTAM

Mechanism of Action

Ceftolozane (Zerbaxa, Cubist Pharmaceuticals, Lexington, Mass) is an extended spectrum cephalosporin in combination with tazobactam, a beta-lactamase inhibitor that was approved in December 2014. This is the first cephalosporin to be combined with a beta-lactamase inhibitor. Cephalosporins (a beta-lactam antibiotic) bind to penicillin-binding proteins and inhibit bacterial cell wall synthesis. Ceftolozane has greater affinity for penicillin-binding proteins than either ceftazidime or imipenem, making it more potent than these agents for certain pathogens. Tazobactam binds to some beta-lactamases (enzymes) and renders the enzyme unable to hydrolyze the beta-lactam ring, thus maintaining the antimicrobial activity of the antibiotic.[5-7]

Clinical Microbiology

Ceftolozane/tazobactam demonstrates activity against many Gram-negative bacteria, including *Pseudomonas aeruginosa*. In vitro data suggest that the addition of the beta-lactamase inhibitor enhances its Gram-negative activity against some extended spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae (including ceftazidime-resistant Enterobacteriaceae), as well as increased stability to AmpC beta-lactamases. However, ceftolozane/tazobactam does not have activity against metallo beta-lactamases or carbapenemase-producing bacteria. In the phase 3 intra-abdominal study, a small subset of patients (150 patients) had ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*. In the trial, patients treated with ceftolozane/tazobactam had clinical cure rates of 97% as compared with 85% of patients treated with meropenem. Ceftolozane alone has potent in vitro anti-pseudomonal activity, including multidrug-resistant *P aeruginosa*. Ceftolozane/tazobactam has coverage against some Gram-positive bacteria as well. It has activity against some *Streptococcus* species, but has only limited coverage against *Staphylococcus* spp. In addition, it should not be used for infections secondary to *Enterococcus* spp. Data suggest limited anaerobic activity as well, but it should be used in combination with metronidazole for the treatment of complicated intra-abdominal infections (or other infections in which anaerobes are likely).[5-10]

Indications

Ceftolozane/tazobactam is FDA approved for the treatment of complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis.[6] A study evaluating its use in ventilator-associated pneumonia is currently underway. With regard to complicated intra-abdominal infections, ceftolozane/tazobactam in combination with metronidazole was compared with meropenem for a duration of 4-14 days and was found to be noninferior (83% and 87.3%, respectively). In the complicated urinary tract infections trials, ceftolozane/tazobactam was compared with levofloxacin for a duration of 7 days. Levofloxacin resistance was noted in almost 27% of patients; however, when these patients were removed from the analysis, ceftolozane/tazobactam was also found to be noninferior (82.6% efficacy with ceftolozane/tazobactam vs. 79.7% with levofloxacin).

Data from both the complicated intra-abdominal and urinary tract infections trials demonstrate that patients with a creatinine clearance (CrCl) of 30-49 mL/min had lower cure rates versus the comparator groups (meropenem and levofloxacin, respectively). In the intra-abdominal study, the clinical cure rate with CrCl 30-49 mL/min for ceftolozane/tazobactam was 47.8% and 69.2% for meropenem. These data come from a subgroup analysis of a small number of patients. It is important to note that all patients in the subgroup with CrCl 30-49 mL/min (regardless of treatment arm) had lower cure rates than the subgroup with CrCl $\geq$ 50 mL/min (with clinical cure rates of 85.2% and 87.9%, respectively, for ceftolozane/tazobactam and meropenem in the intra-abdominal study). In response, the FDA has recommended that additional studies be conducted evaluating outcomes in patients with CrCl of $<$ 50 mL/min. In addition, in the intra-abdominal infections trials, clinical cure rates were noted to be lower in patients $\geq$ 65 years old who received ceftolozane/tazobactam compared with those given meropenem (69% vs. 82.4%). Again, the FDA has