Doripenem: A New Carbapenem in the Treatment of Nosocomial Infection

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Difficult-to-treat infections caused by gram-negative pathogens are common in the hospital setting, particularly those caused by *Pseudomonas aeruginosa*, *Acinetobacter* species, and extended-spectrum β-lactamase–producing Enterobacteriaceae, all of which are capable of developing resistance to common antimicrobial agents. New drugs are urgently needed to combat this threat. In this supplement, researchers in infectious diseases discuss the role of doripenem, a newly approved carbapenem, in the treatment of serious nosocomial infections and review new data on doripenem for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia. The topics addressed include antimicrobial resistance and the available therapeutic options against gram-negative pathogens, the in vitro activity of doripenem, the efficacy and safety of intravenous infusion of doripenem, and the clinical and economic consequences of ventilator-associated pneumonia. Based on the strength of the clinical evidence presented, doripenem appears to provide broad-spectrum coverage and antipseudomonal activity, leading to advantageous clinical outcomes, particularly in patients at risk of infection with drug-resistant pathogens.

As clinicians are faced with a paucity of effective antimicrobial agents, they are at the same time challenged with increasing numbers of drug-resistant pathogens in the hospital setting. There is an urgent need for new agents to combat this threat. Although much of the recent drug development has been focused on treatment of drug-resistant gram-positive infections, doripenem, a newly approved carbapenem, has emerged to combat a growing medical threat: increased drug resistance among gram-negative pathogens. Physicians are frequently confronted with infections caused by *Pseudomonas aeruginosa*, *Acinetobacter* species, and extended-spectrum β-lactamase–producing Enterobacteriaceae, all of which are problematic gram-negative pathogens that frequently exhibit resistance to currently available antimicrobial agents. Carbapenems, including doripenem, demonstrate the broadest spectrum of activity among the β-lactam antimicrobials, providing coverage against gram-positive, gram-negative, and anaerobic bacterial pathogens. Because carbapenems continue to be a mainstay of empirical therapy for hospitalized patients with serious infection, including nosocomial infection, doripenem may extend the usefulness of the class by virtue of several features and characteristics that broaden its antimicrobial spectrum beyond that of other carbapenems, thus covering more gram-negative pathogens with a higher minimum inhibitory concentration, particularly *P. aeruginosa* and *Acinetobacter* species.

In May 2008, a panel of infectious diseases researchers was convened to discuss the role of doripenem in the treatment of serious infections and to review new data on doripenem for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP). The participants in this roundtable discussion covered a number of topics, including antimicrobial resistance and the available therapeutic options against gram-negative pathogens, including a critical review of the in vitro activity, safety, and efficacy of doripenem. Finally, the participants considered the clinical and economic consequences of VAP in light of changing re-
imbursement plans and the implications of doripenem in this evolving critical care environment.

In this supplement of Clinical Infectious Diseases, Rahal [1] reviews the growing problem of increasing antimicrobial resistance among gram-negative bacilli and its impact on the treatment of infections caused by such bacterial pathogens. Antimicrobial resistance is increasing among Acinetobacter species, extended-spectrum β-lactamase–producing Enterobacteriaceae, and P. aeruginosa, all of which are gram-negative pathogens associated with a variety of infections, particularly among patients in the intensive care unit. The diminished susceptibility of these bacteria to antibiotics currently recommended for empirical treatment leaves physicians with few options for effective therapy. The mechanisms by which resistance develops in gram-negative bacilli are complex and continually evolving. For example, P. aeruginosa and other nonfermenting gram-negative bacteria, such as Acinetobacter baumannii, have high intrinsic resistance to antimicrobials because of their low outer-membrane permeability, coupled with secondary resistance mechanisms, such as antibiotic efflux pumps and inducible β-lactamase production. In addition to having chromosomally encoded β-lactamases (AmpC cephalosporinases), both P. aeruginosa and A. baumannii have the ability to acquire genes that encode other β-lactamases, conferring resistance to most β-lactam antibiotics. Resistance to carbapenems is currently limited and mostly confined to P. aeruginosa and A. baumannii, in which multiple resistance mechanisms differentially affect the potency of agents in the carbapenem class. The recent emergence of some isolates that are intrinsically resistant to carbapenems on the basis of the production of metallo-β-lactamases is particularly problematic, because these enzymes confer resistance to the most potent class of β-lactams, a class traditionally reserved for treatment of the sickest patients. The prevalence of β-lactamase–mediated resistance in nonfermentative gram-negative bacteria is increasing. Once the encoding genes are acquired, carbapenemases confer the ability to hydrolyze all drugs in the β-lactam class, producing multidrug-resistant isolates and, thus, seriously limiting therapeutic options.

Because clinical evidence indicates that the choice of inappropriate initial therapy is associated with increased mortality and increased costs to health care systems [2], it is imperative that patients with serious infection receive appropriate initial empirical treatment with a potent, broad-spectrum antibiotic regimen that provides coverage against any drug-resistant organisms that are likely to be causative pathogens. Recent surveillance data indicate that the carbapenems, including doripenem, offer a broad spectrum of activity and are highly active against most Enterobacteriaceae strains and many P. aeruginosa and A. baumannii strains.

Sahm [3] reviews the in vitro antimicrobial activity of doripenem against a wide range of gram-negative and gram-positive pathogens. The in vitro data indicate that doripenem has the intrinsic activity of imipenem against gram-positive organisms and of meropenem against gram-negative organisms. Doripenem showed potent in vitro activity against isolates of Enterobacteriaceae and P. aeruginosa, which are gram-negative pathogens with increased capacity for antimicrobial resistance. Doripenem has been shown to have potent inhibitory effects against P. aeruginosa isolates (including difficult-to-treat strains), with a minimum inhibitory concentration that is 2–4 times lower than that of imipenem and meropenem. The in vitro studies demonstrate that doripenem is less likely to select for carbapenem-resistant mutants within bacterial populations than are the other carbapenems [4, 5].

Greater in vitro activity, however, does not necessarily translate to greater in vivo success. Clinical efficacy must be established in prospective, randomized, controlled clinical trials. Restrepo [6] reviews published clinical experience with doripenem and reports the clinical outcomes for several indications in patients with difficult-to-treat infections caused by P. aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae, and Escherichia coli. The doripenem VAP trial, which is reported to be the largest completed phase 3 study involving patients with VAP, is a head-to-head comparison of doripenem with imipenem [7]. Emerging results from post hoc analyses of data from the nosocomial pneumonia and VAP studies show that clinical cure rates with doripenem among certain populations at high risk of infection, such as those with high Acute Physiology and Chronic Health Evaluation II scores and those infected with P. aeruginosa, are noninferior to the cure rates among comparator populations in 2 large phase 3 clinical studies [8]. Based on the strength of its broad-spectrum coverage and antipseudomonal activity, doripenem shows promise as initial therapy for nosocomial pneumonia and VAP, particularly among patients at risk of infection with resistant pathogens.

Redman and File [9] reviewed the safety data from doripenem clinical trials for nosocomial pneumonia and VAP, complicated intra-abdominal infections, and complicated urinary tract infections and found that the overall adverse event profile of doripenem was comparable to that of other carbapenems. Because treatment-emergent seizures were observed when imipenem was given at high doses (1.0 g every 6 h), the neurotoxic potential and convulsive activity of a new carbapenem or other β-lactam antibiotic are of concern. Preclinical testing of doripenem revealed an absence of convulsive activity in several animal models, and relative to other β-lactams, doripenem showed a low affinity for binding to the γ-aminobutyric acid receptor in vitro, suggesting that doripenem may have a low potential for neurotoxic effects. In terms of clinical data, there were no treatment-emergent seizures associated with the use of doripenem in 7 phase 2 or 3 clinical trials. Although continued clinical surveillance is needed, the preclinical models...
and phase 3 experience with doripenem suggest that higher doses can be given and may be appropriate for treatment of some infections.

One of the more challenging nosocomial infections in the intensive care unit is VAP, which is frequently caused by *P. aeruginosa*, *Acinetobacter* species, or *Enterobacteriaceae*, all of which are gram-negative pathogens with increasing rates of resistance to currently available antimicrobial agents. Amin [10] reviews the health care costs associated with the development of drug resistance in gram-negative organisms and the economic burden this development imposes on hospital systems, which is a critical issue in today’s health care environment. An in-depth look at medical resource use in a prospective phase 3 trial of doripenem versus imipenem for the treatment of VAP showed that the duration of hospital stay and the duration of use of mechanical ventilation were significantly shorter for patients who received doripenem than for those who received imipenem [11]. The reduced use of hospital resources that was observed with doripenem was associated with a substantial cost savings, offering a potential economic benefit to hospitals. The reduced duration of hospital stay not only may lead to a reduction in total health care costs but also may minimize patient exposure to drug-resistant organisms, use of additional antibiotics, and the number of complications associated with prolonged hospitalization.

The body of evidence presented here is relevant to clinical practice and serves as a starting point for optimizing the use of carbapenems for the treatment of serious gram-negative infections. Doripenem has demonstrated significant efficacy among patients with a high Acute Physiology and Chronic Health Evaluation II score and advantageous clinical outcomes in patients with difficult-to-treat gram-negative infection. In addition to its clinical benefits, doripenem has demonstrated favorable economic outcomes, substantially reducing the duration of hospital stay and the duration of mechanical ventilation use for patients with VAP [11]. I hope that the information provided in this supplement will help physicians to become aware of a new antimicrobial option for the treatment of serious infections, including nosocomial infections, in hospitalized patients.

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