Ceftaroline Noninferior to Vancomycin/Aztreonam

BY KERRI WACHTER

WASHINGTON — The investigational antibiotic ceftaroline was found to be effective against a range of gram-positive and gram-negative organisms that can cause complicated skin and skin structure infections, according to data from a phase III noninferiority study of more than 600 patients.

Clinical cure rates (8-15 days after the end of therapy) were similar for patients who received at least one dose of ceftaroline or vancomycin/aztreonam (the modified intent-to-treat population)—87% for those on ceftaroline and 86% for those on vancomycin-aztreonam, according to data from the CANVAS-1 study presented as a poster at the jointly held annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the annual meeting of the Infectious Diseases Society of America.

"Ceftaroline monotherapy was as effective and well tolerated as vancomycin plus aztreonam combination therapy in treating patients with complicated skin and skin structure infections due to both gram-positive and gram-negative pathogens," reported Dr. Ralph Corey of Duke University, Durham, N.C., and his coinvestigators.

The study was supported by Forrest Laboratories Inc., which is developing ceftaroline. Two of Dr. Corey's coinvestigators are employed by Cerexa Inc., wholly owned subsidiary of Forrest. Dr. Corey disclosed receiving research funding and serving as an adviser to Cerexa.

The double-blind study randomized patients to either 600 mg intravenous ceftaroline every 12 hours for 5-14 days or 1 g intravenous vancomycin plus 1 g intravenous aztreonam (Azactam) every 12 hours for 5-14 days. Aztreonam was discontinued if gram-negative pathogens were not identified or suspected.

At enrollment, 353 patients were randomized to receive ceftaroline and 349 were randomized to receive vancomycin/aztreonam. The modified intention-to-treat population included all patients who had received any study drug—351 patients in the ceftaroline group and 347 patients in the vancomycin/aztreonam group.

Almost a quarter of the patients in each group—21% in the ceftaroline group and 25% in the vancomycin/aztreonam group—had polymicrobial infection. The most common infection type was deep, extensive cellulitis (35% in both groups), followed by major abscess (28% of the ceftaroline group and 29% of the vancomycin/aztreonam group).

There were 471 patients—244 in the ceftaroline group and 227 in the vancomycin/aztreonam group—who were microbiologically evaluable. Microbiologic eradication was achieved in 92% of patients on ceftaroline and 93% of patients on vancomycin/aztreonam.

Staphylococcus aureus was the most commonly isolated organism. But ceftaroline was effective against a range of gram-positive and gram-negative organisms. (See box.)

Most adverse events were mild—72% for both groups. The most common adverse event in the ceftaroline group was nausea (5.7%), followed by headache (5.1%). The most common adverse event in the vancomycin/aztreonam group was pruritus (8.4%).

"Ceftaroline has the potential to provide a monotherapy option for the treatment of complicated skin and skin structure infections," the investigators wrote. ■

Clinical Cure by Organism

	Ceftaroline	Vanco/Az
Gram-positive		
Staphylococcus aureus	93%	95%
MRSA	95%	95%
MSSA	91%	95%
Streptococcus pyogenes	100%	100%
Streptococcus agalactiae	93%	100%
Enterococcus faecalis	93%	92%
Gram-negative		
Escherichia coli	90%	87%
Klebsiella pneumoniae	91%	100%
Proteus mirabilis	70%	90%
Pseudomonas aeruginosa	100%	90%

Note: Based on a study of 244 patients who received ceftaroline and 227 who received vancomycin/aztreonam (vanco/az).

Source: Dr. Corey

THE EFFECTIVE PHYSICIAN

Monitoring Vancomycin

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Vancomycin has a reputation for potential nephro- and ototoxicity and is increasingly used in the inpatient setting. The American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists have issued a new report to guide the management of patients on this useful antimicrobial.

Conclusions

Known as "Mississippi Mud" 50 years ago because impurities gave its solution a brownish color, vancomycin is now a more pure formulation and has a far lower incidence of nephro- and otoxicity when used as a sole agent.

Concomitant administration with an aminoglycoside may increase risk of nephrotoxicity three- to fourfold.

Common side effects such as phlebitis, chills, and fever are not related to serum concentration. Doses over 1 g should be infused over a period of 1.5-2.0 hours, as too-rapid infusion can cause histamine release and the "red man syndrome."

Vancomycin is cidal for gram-positive pathogens such as *Staphylococcus aureus* and *S. epidermatis* independent of serum concentration. In vivo, it is approximately 50% protein bound.

Penetration into cerebrospinal fluid is aided by inflammation of the meninges. Tissue concentration in the skin is diminished in diabetic patients. Drug concentration in lung tissue is substantially less than half the serum concentration.

Vancomycin has been well studied and many of its pharmacodynamic parameters identified. The area under the curve (AUC) is obtained by plotting serum concentration vs. time after dosing vancomycin. The AUC/minimum inhibitory concentration (MIC) ratio has emerged as the best parameter for measuring vancomycin's effectiveness against all *S. aureus,* including methicillin-resistant *S. aureus* (MRSA) and strains that are intermediate-susceptible to vancomycin.

Serum trough levels are a rough approximate to the AUC/MIC ratio.

Genetic studies indicate that intermediate-susceptible *S. aureus* strains have an accessory gene regulator (*agr*). Approximately half of hospital-acquired MRSA infections have the *agr* locus, which increases potential for resistance to vancomycin four- to five-fold.

Implementation

Unlike β-lactase agents, which have short half-lives, vancomycin is not more effective with continuous infusion or more frequent administration. Its cidal activity is slower than that of β-lactams, and inoculum size can challenge effectiveness and result in a delayed clinical response.

There is little clinical value for routine measurement of peak serum concentration of vancomycin because there is no correlation with toxicity.

Maximal clinical effectiveness of vancomycin is achieved when an AUC/MIC ratio over 400 is reached.

Serum trough levels have been used as a surrogate marker for AUC/MIC ratio and should be obtained just prior to a new dosing of the medication. The first trough level of vancomycin should be obtained after achieving steady-state serum concentration (usually after the fourth dose). Regular monitoring of trough levels is indicated only for patients who are on prolonged therapy or receiving aggressive dosing to combat a serious infection, or who have unstable renal function.

Traditional trough levels of 5-10 mg/L are likely too low to ensure effective vancomycin exposure and can reduce susceptibility to the drug. It is recommended to maintain trough levels above 10 mg/L to avoid development of resistance.

Giving 1 g of vancomycin every 12 hours will achieve an AUC/MIC over 400 only when the MIC is less than 0.5 mg/L.

For organisms with an MIC of 1 mg/L, clinicians should target a trough level of 15 mg/L to maximize the likelihood of achieving therapeutic effectiveness. This trough level would require 12-15 mg/kg of the drug every 8-12 hours (or 3-4 g/day in divided doses) in patients with normal renal function.

To rapidly achieve target therapeutic levels in seriously ill patients, a loading dose of 25-30 mg/kg given over 1.5-2.0 hours should be considered.

It is probably not possible to achieve an AUC/MIC over 400 in patients infected with organisms that have a vancomycin MIC of 2 mg/L and above. Alternative therapy should be considered.

Trough levels of 15-20 mg/L have been recommended by the American Thoracic Society for patients with normal renal function and serious chest infections. There are little data to verify safety at this level of chronic exposure.

Reference

Rybak M, et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am. J. Health Syst. Pharm. 2009;66:82-98.

DR. GOLDEN *(left) is professor of medicine and public health and* DR. HOPKINS *is program director for the internal medicine/pediatrics combined residency program at the University of Arkansas, Little Rock. Write to Dr. Golden and Dr. Hopkins at our editorial offices or imnews@elsevier.com.*