FDA Grants New Cephalosporin Fast-Track Status

BY BRUCE K. DIXON
Chicago Bureau

Monotherapy with ceftobiprole was found to be as effective as vancomycin plus ceftazidime for treating patients with a broad range of complicated skin and skin-structure infections caused by gram-positive and gram-negative bacteria.

Following the completion of successful phase III registration trials, the Food and Drug Administration granted ceftobiprole fast-track status for the treatment of both complicated skin and skin-structure infections caused by methicillin-resistant staphylococci and hospital-acquired pneumonia.

Ceftobiprole is a novel, broad-spectrum cephalosporin developed jointly by Basilea Pharmaceutica AG and Cilag AG International (a Johnson & Johnson company).

The randomized, double-blind, multicenter trial included 828 patients with diabetic foot infections, abscess, cellulitis, and wound infection, reported Gary J. Noel and his fellow researchers, all full-time employees of Johnson & Johnson Pharmaceutical Research and Development, Raritan, N.J., which funded the study (Clin. Infect. Dis. 2008;46:647-55).

Infecting pathogen types—identified in at least 10 patients at baseline—included coagulase-negative and coagulase-positive staphylococci, *Pseudomonas aeruginosa*, β-hemolytic streptococci, and enterobacteriaceae. The most prevalent pathogens were gram-positive bacteria, specifically methicillin-resistant *Staphylococcus aureus* (MRSA) (123 patients) and methicillin-susceptible *S. aureus* (MSSA) (250 patients).

The patient cohort, accumulated over 129 international sites, was divided into two arms, with 547 patients receiving ceftobiprole and 281 receiving the glycopeptide antibiotic vancomycin plus the third-generation cephalosporin ceftazidime, according to the researchers.

Patients in the ceftobiprole arm received 500 mg for 120 minutes every 8 hours, while in the comparator group, the starting dose was 1,000 mg vancomycin infused over 60 minutes every 12 hours plus 1,000 mg ceftazidime infused over 120 minutes every 8 hours.

The mean duration of treatment in the clinically evaluable population was about 9 days in both arms, the authors noted.

At the investigating physicians' discretion, empirical treatment with metronidazole (Flagyl, Pfizer) was permitted to provide activity against anaerobic bacteria. The nitroimidazole anti-infective was given to 39 of the ceftobiprole-treated patients and 17 of the comparator-treated patients, the researchers wrote.

At the test-of-cure (TOC) visit (after 6-17 days of treatment) for the evaluable patients, clinical cure occurred for 439 of 485 (91%) ceftobiprole-treated patients and for 220 of 244 (90%) comparator-treated patients, the researchers noted, adding that cure rates in the intent-to-treat population at the TOC visit were about 81% in both groups.

The cure rates exceeded 90% among ceftobiprole-treated patients with abscess, cellulitis, or wound infections, and among patients who had surgical debridement of their infections performed within 48 hours after study enrollment, the authors reported, adding that these rates were comparable with those observed among comparator-treated patients.

Among patients with *S. aureus*, MRSA, and MSSA infections, cure rates at the TOC visit among ceftobiprole-treated patients and among comparator-treated patients were also comparable.

The difference in cure rates of complicated skin and skin-structure infections associated with bacteremia was not statistically significant.

Among the 30 ceftobiprole-treated individuals from whom *P. aeruginosa* was isolated at baseline, 26 (87%) were clinically cured, according to the researchers. Among the 12 ceftobiprole-treated patients from whom *P. aeruginosa* was isolated as the sole pathogen at baseline, 9 (75%) were determined to be clinically cured at the TOC visit.

In an accompanying editorial, Dr. Andreas F. Widmer concurred with the researchers and noted that for infections involving enterobacteriaceae, ceftobiprole may become the drug of choice if currently unknown adverse effects do not limit its use in the future (Clin. Infect. Dis. 2008;46:656-8).

MRSA coverage with ceftobiprole may improve outcomes in complicated skin and skin-structure infections by enabling early bactericidal therapy in patients admitted to emergency departments with infections not yet identified as being caused by MRSA, said Dr. Widmer of the division of infectious disease and hospital epidemiology at University Hospital in Basel, Switzerland.

"This promising new agent may be regarded as the first clinically effective cephalosporin against MRSA for treatment of complicated skin and skin-structure infections, with two randomized clinical trials supporting its efficacy," he said, referring to a trial published this year by the same group of investigators that compared ceftobiprole with vancomycin alone (Antimicrob. Agents Chemother. 2008;52:37-44).

Dr. Widmer has been a member of an expert group for Novartis and has served on the advisory board for Arpida Ltd. ■

Gonorrhea Treatment 'Hanging by a Thread'

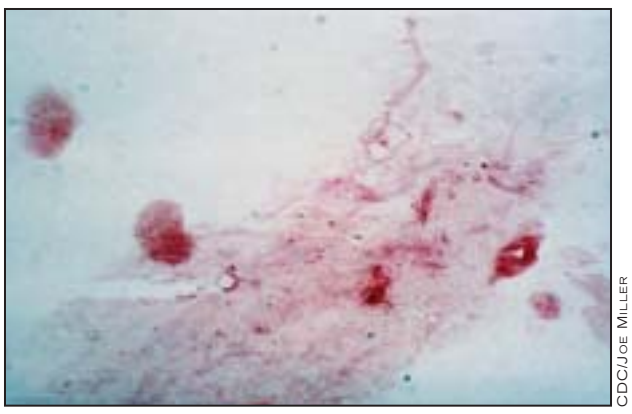
BY BETSY BATES
Los Angeles Bureau

SAN DIEGO — Resistance to gonorrhea drugs is climbing just as treatment options are dwindling, making for a potential public health crisis if more drug choices are not brought to market soon.

"The situation is really not good. We're hanging by a thread, with a very serious resistance problem. If we lose cephalosporins [to resistance], we will really be up a creek," Dr. Jeanne Marrazzo said at Perspectives in Women's Health, sponsored by FAMILY PRACTICE NEWS, OB.GYN. NEWS, and INTERNAL MEDICINE NEWS.

Practically speaking, ceftriaxone (125 mg intramuscularly, in a single dose) remains the only available regimen recommended by the Centers for Disease Control and Prevention for treating gonorrhea, the second-most commonly reported infectious disease in the United States. After years of decline or stability, U.S. gonorrhea rates rose for the second straight year in 2006, with about 358,000 new cases reported, according to CDC surveillance statistics.

Many physicians are wary of dependence on a single drug to treat a widespread infectious disease because of possible resistance, and gonorrhea seems particularly susceptible, Dr. Marrazzo said. Widespread resistance long ago took penicillins, sulfa drugs, tetracycline, and spectinomycin off the table for gonococcal infections; by April of last year, fluoroquinolones, including ciprofloxacin, ofloxacin, and levofloxacin, also lost their "recommended" status because of resistance documented in sites in the United States and other countries. Cefixime remains on the CDC's recommended list; however, it is currently unavailable in the United States, except in a liquid pediatric formula approved last year.



CDC/JOE MILLER

This cervical smear shows extracellular diplococci that were determined to be *Neisseria gonorrhoeae*.

Dr. Marrazzo explained that Wyeth Pharmaceuticals discontinued manufacture of cefixime tablets, once marketed as Suprax, when the drug's patent expired in 2002. Exclusive rights to the drug are now held by a company based in India, which is rumored to be working with the Food and Drug Administration to obtain approval to market 400-mg tablets in the United States.

Alternative regimens suggested by the CDC include spectinomycin, which is also no longer being manufactured in the United States, and single-dose cephalosporin regimens.

All patients with gonorrhea should be cotreated for chlamydia unless it is ruled out with a highly sensitive test.

The lack of availability of spectinomycin complicates management of patients allergic to cephalosporins, according to Dr. Marrazzo of the Seattle STD/HIV Prevention Training Center and the University of Washington, Seattle. The CDC "cluelessly" recommends desensitizing patients.

Such cases might call for special consideration of high-dose azithromycin, but the 2-g dose required can cause gastrointestinal problems, even with split doses. In any case, resistance to azithromycin is likely increasing, so "that's going to be a short-term fix," she said. If fluoroquinolones are the only remaining option in cephalosporin-allergic patients, Dr. Marrazzo recommends obtaining a culture before treatment to ensure sensitivity, or obtaining a test of cure in 3-5 days by culture or 3 weeks if a nucleic acid amplification test is used.

Dr. Marrazzo disclosed that she is a consultant to Mission Pharmacal and serves on the speakers bureaus of 3M and Merck & Co. Perspectives in Women's Health and this newspaper are owned by Elsevier. ■

Norovirus Was Spread Via School Computers

An outbreak of norovirus in a District of Columbia elementary school last year was probably transmitted by unclean computer mice and keyboards.

The Centers for Disease Control and Prevention was notified after 27 students and two staff members experienced symptoms of gastroenteritis (defined as nausea, vomiting, or diarrhea) within a 4-day period.

After inspecting the classrooms, CDC staff administered questionnaires to all staff and students. Results showed that students assigned to one particular first-grade classroom had almost double the risk of gastroenteritis during the 4-day period (relative risk 1.94). The affected classroom was the one that housed the school's computers, which were shared by students and staff. Foodborne illness was ruled out because no food was served at the school (MMWR 2008;56:1340-3).

Environmental samples taken from a computer mouse and keyboard contained norovirus subtype GII. This strain also was found in stool samples from two persons who had been on the site.

At the CDC's urging, the school cleaned all shared computer surfaces with a bleach solution, and all students and staff were restricted from the school until 72 hours after resolution of their illness to avoid recontamination.

In a commentary, the CDC noted that prior research has shown that norovirus can be transmitted to fomites and that a surrogate marker for norovirus, feline calcivirus, has been shown to survive on computer mice and keyboards for up to 2 days.

—John R. Bell