

46th Interscience Conference on Antimicrobial Agents and Chemotherapy

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San Francisco, California, was the venue for the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held from September 27 to 30, 2006. More than 12,000 physicians, infectious-disease specialists, and other health care professionals heard the latest developments in the treatment and prevention of infectious diseases.

Approaches of interest included a broad-spectrum cephalosporin (ceftaroline) compared with a gold-standard agent (vancomycin) for skin and skin-structure infections; a potent ketolide (cethromycin) for acute bacterial exacerbations of



chronic bronchitis; a glycyglycine (tigecycline) compared with a fluoroquinolone (levofloxacin) for community-acquired pneumonia; a cephalosporin (ceftobiprole) for skin infections; a fluoroquinolone (moxifloxacin) for leprosy; a ketolide (telithromycin) compared with a standard penicillin-based therapy in acute bacterial sinusitis; oseltamivir to reduce pneumonia risk following

pediatric influenza; a human papillomavirus vaccine (Gardasil) for preventing virus-related precancerous lesions and genital warts; and an antifungal agent (micafungin) for invasive candidiasis in children.

Ceftaroline for Skin and Skin-Structure Infections

Speaker: Dirk A. Thye, MD, Vice President, Clinical Development, Cerexa, Inc., Alameda, California

Ceftaroline (Cerexa, Inc.), a next-generation, broad-spectrum, injectable cephalosporin that combines the advantages of an enhanced gram-positive spectrum, including anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity with extensive gram-negative activity. It was efficacious and well tolerated in patients with complicated skin and skin-structure infections (cSSSIs).

In a randomized, observer-blinded, phase 2 multicenter study, 100 hospitalized adults with local and systemic symptoms of cSSSI were randomly assigned, in a 2:1 fashion, to receive ceftaroline 600 mg (67 patients) or the gold-standard comparator vancomycin 1 g (Vancocin, Eli Lilly) (32 patients). Vancomycin was administered with or without adjunctive aztreonam (Azactam, Elan), and both test drugs were given intravenously every 12 hours for seven to 13 days. Assessments included clinical and microbiological response, adverse drug effects (ADEs), and laboratory test results. The primary outcome measure was the post-therapy clinical cure rate at seven to 14 days.

The clinical cure rate for the evaluable patients was 96.7% (59/61) with ceftaroline and 88.9% (24/27) with standard comparator therapy. Responses for the microbiologically evaluable patient population were 95.2% (in 40 of 41 patients) with ceftaroline and 85.7% (in 18 of 21 patients) with standard therapy.

Ceftaroline also demonstrated excellent *in vitro* activity against gram-positive and gram-negative organisms isolated from patients in the study, including 100% of MRSA isolates inhibited at 0.5 mg/liter or less.

In this phase 2 trial, ceftaroline displayed a favorable ADE profile consistent with the established safety profile of the cephalosporin class, and most side effects were mild in nature. The most common ADE observed with ceftaroline was mild headache. No serious ADEs were observed in this group of patients. ADEs typically associated with vancomycin were reported for the comparator group, including interstitial nephritis-related renal failure and the "red man syndrome."

Cethromycin Useful against Acute Bacterial Exacerbation of Chronic Bronchitis

Speaker: Michael L. Leski, PhD, Senior Medical Writer, Advanced Life Sciences, Woodridge, Illinois

Cethromycin (ALS-920, Advanced Life Sciences/Abbott), a second-generation ketolide antibiotic active against clinically important gram-positive bacteria (including macrolide-resistant strains), was effective in the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB).

A double-blind, randomized, parallel-group, multicenter phase 2 study enrolled 384 patients with a presumptive diagnosis of ABECB. Patients received one of three doses of cethromycin, in a 1:1:1 ratio; 126 patients received cethro-

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mycin 150 mg once daily, 129 patients received 300 mg once daily, and 129 patients received 600 mg once daily. All of the patients were treated for five days.

Clinical cure was defined as the resolution of at least one clinical symptom of ABECB (e.g., dyspnea, sputum volume, purulence, cough, or fever), with improvement in at least half of the other symptoms. The investigators also assessed bacteriological cure rates and overall pathogen eradication rates.

All three treatments helped in eradicating the target pathogens and in resolving symptoms of ABECB. Cure rates with cethromycin in the clinically evaluable patients were 87% (99/114) at a dose of 150 mg, 90% (105/117) at 300 mg, and 90% (101/112) at 600 mg. The bacteriological cure rates in the clinically evaluable patients were 86% (43/60) at a dose of 150 mg, 88% (49/56) at 300 mg, and 92% (58/63) at 600 mg.

The most common ADEs were diarrhea, taste perversion, and nausea. The incidence of these events appeared to increase with the dose.

The increased incidence of gastrointestinal (GI) ADEs at 600 mg, as well as the lower efficacy observed at 150 mg, may support the selection of a 300-mg dose of cethromycin for patients with ABECB in future studies.

Tigecycline for Community-Acquired Pneumonia

Speaker: Gary Dukart, MD, Senior Director, Clinical Research and Development, Wyeth, Collegeville, Pennsylvania

Tigecycline (Tygacil, Wyeth), a first-in-its-class glycylcycline antibiotic, provided clinical and microbiological cure rates comparable (i.e., non-inferior) to those of levofloxacin (Levaquin, Ortho-McNeil) in hospitalized patients with community-acquired pneumonia (CAP).

This finding was assessed from integrated results from two multicenter, double-blind phase 3 studies. Overall, 846 patients were included in the clinical modified, intent-to-treat (c-mITT) populations; 424 patients randomly received tigecycline 100 mg IV initially, followed by 50 mg every 12 hours, and 422 received levofloxacin 500 mg IV once daily or every 12 hours. In one study, patients could be switched to oral levofloxacin after three days of IV treatment at the physician's discretion.

The co-primary efficacy endpoints were the clinical response at the test-of-cure (TOC) assessment in the clinically evaluable and c-mITT patients. Safety was assessed in the c-mITT population. From this population, 574 patients were clinically evaluable; 282 received tigecycline, and 292 received levofloxacin.

In the clinically evaluable population, 89.7% of the patients were cured with tigecycline and 86.3% of the patients were cured with levofloxacin. For the c-mITT population, the cure rates were 81.7% with tigecycline and 79.7% with levofloxacin.

Non-inferiority was demonstrated in both groups ($P < .001$). Microbiological responses at the test-of-cure assessment were also similar between the two treatment groups at both the patient level and by the isolate at the baseline.

With regard to safety profiles of the two antibiotics, statistically significant differences were reported with tigecycline and levofloxacin for nausea (20.8% vs. 6.6%) and vomiting (13.2% vs. 3.3%). Liver abnormalities, in contrast, occurred more often with levofloxacin than with tigecycline:

- aspartate transaminase (AST, SGOT): 5.9% with levofloxacin, 2.1% with tigecycline
- alanine transaminase (ALT, SGPT): 6.4% with levofloxacin, 2.6% with tigecycline

Ceftobiprole Fights Methicillin-Resistant *S. aureus* Infections

Speaker: Gary Noel, MD, Senior Director, Clinical Research, and Clinical Leader, Infectious Diseases, Johnson & Johnson Pharmaceutical Research and Development, LLD, Raritan, New Jersey

Ceftobiprole (J&J/Basilea), a broad-spectrum cephalosporin with activity against MRSA, was comparable in efficacy to vancomycin as standard therapy in patients with cSSSIs caused by gram-positive bacteria, 25% of which were MRSA.

A total of 784 patients with cSSSIs, in whom gram-positive pathogens were documented or suspected on the basis of microscopic examination, were enrolled in a large, multicenter, randomized, double-blind phase 3 trial. Enrollment was stratified by patient type; 48% had abscesses, and 33% had wound infections. Patients were given ceftobiprole 500 mg every 12 hours or vancomycin 1 g every 12 hours. The primary objective was to compare clinical cure rates seven to 14 days after the completion of therapy.

The overall cure rate with ceftobiprole ($n = 282$ patients) was 93.3%; the rate with vancomycin ($n = 277$ patients) was 93.5%. Cure rates in the clinically evaluable populations with MRSA infections were 91.8% with ceftobiprole therapy ($n = 61$ patients) and 90% with vancomycin ($n = 60$ patients).

Ceftobiprole was well tolerated, with few serious treatment-related ADEs and few discontinuations of therapy caused by treatment-related ADEs. Serious treatment-related ADEs were reported in 1% of the ceftobiprole patients and in 3% of the vancomycin group.

As for non-serious ADEs, more mild taste disturbances and nausea were noted in the ceftobiprole-treated patients, whereas the vancomycin patients had more skin rashes and disturbed renal function.

Moxifloxacin Shows Promise against Leprosy

Speaker: Robert H. Gelber, MD, Infectious Disease Specialist in Leprosy, Leonard Wood Memorial Center for Leprosy Research, San Anselmo, California

In the first trial of the fluoroquinolone moxifloxacin (Avelox, Bayer) for patients with lepromatous leprosy (Hansen's disease), improvement in clearing skin lesions caused by *Mycobacterium leprae* was more rapid than with other antibiotics used to treat leprosy (including other fluoroquinolones) without serious ADEs or toxicities. Patients with the lepromatous type lack resistance, and all tissues are affected.

Ten men with untreated lepromatous leprosy, all from a leprosy-endemic area in the Philippines, were enrolled in the trial. They were given moxifloxacin with a single, initial oral dose of 400 mg, followed by no therapy for seven days, and then a single 400-mg oral dose from the eighth day to the 56th day. Each patient was hospitalized throughout the treatment period and was observed to ensure adherence to the drug regimen.

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Using serial clinical photographs, toxicity profiles, and the extent of eradication of *M. leprae*, the investigators also evaluated the men for clinical responses. Serial skin biopsy specimens of *M. leprae* were taken on days 0, 7, 14, 28, and 56, and they were tested in mice for viability. Improvement in skin lesions, as demonstrated from the photographs, was evident after two weeks of daily moxifloxacin therapy. This clinical response was much more rapid than that noted previously with other drugs that had been commonly used or under study for the treatment of leprosy, including minocycline (e.g., Minocin, Wyeth), pefloxacin, ofloxacin (e.g., Floxin) and even rifampin.

As observed in mice, the biopsy results on the seventh day showed complete eradication of *M. leprae* after the initial single dose of moxifloxacin in nine of the 10 patients studied and in all 10 men by three weeks of daily therapy. No serious ADEs were observed during the active period of the trial, and none of the patients discontinued therapy.

Telithromycin in Acute Bacterial Sinusitis

Speaker: Martin DesRosiers, MD, Adjunct Professor, Department of Otolaryngology and Allergy, Montreal General Hospital, McGill University; and Head, Section of Rhinology and Paranasal Sinus Diseases, Department of Otolaryngology, Centre Hospitalier, University de Montreal, Montreal, Quebec, Canada

In a comparison study of telithromycin (Ketek, Sanofi-Aventis) and amoxicillin/clavulanate (Augmentin, GlaxoSmith-Kline), treatment of acute bacterial sinusitis with Ketek resulted in clinical efficacy comparable to that of Augmentin but with a shorter time to resolution of symptoms and with fewer treatment-emergent ADEs.

A total of 298 patients, older than 18 years of age, with a clinical and radiological diagnosis of acute bacterial sinusitis were enrolled into a multinational, randomized open-label, non-inferiority study to compare the clinical efficacy, time to symptom resolution, and tolerability of a five-day regimen of Ketek, the first of the ketolides, with a 10-day regimen of Augmentin, an aminopenicillin/beta-lactamase inhibitor. The patients received Ketek 800 mg once daily for five days or Augmentin 875/125 mg twice daily for 10 days. Clinical efficacy and tolerability were determined at the test-of-cure visit at days 17 to 21.

The time to symptom resolution was evaluated via daily patient diary assessments of individual symptoms, including nasal congestion, runny nose, postnasal discharge, thick nasal discharge, and facial pain or pressure. Patients used a six-point scale to rate these symptoms.

Clinical success rates in the per-protocol population, a pre-specified primary endpoint, demonstrated non-inferiority between the two antibiotics: 88.6% in 109 of 123 patients with Ketek and 88.8% in 111 of 125 patients with Augmentin.

The median times to a 50% reduction of total symptom scores, however, were four days with Ketek and five days with Augmentin. The median times to reduction of total symptom scores were six days for Ketek and eight days with Augmentin.

Treatment-emergent ADEs, including those that were not considered treatment-related, occurred in 20.7% of patients receiving Ketek and in 31.8% of those taking Augmentin. These ADEs were mostly gastrointestinal.

Oseltamivir Reduces Secondary Flu Complications

Speaker: Dominick Iacuzio, PhD, Medical Director, Roche Laboratories, Nutley, New Jersey

Oseltamivir (Tamiflu, Roche) effectively reduced the risk of pneumonia and other secondary complications in children from one to 12 years of age when it was administered within one day of an influenza diagnosis.

A retrospective cohort study used health insurance claims data from the 2000–2005 influenza seasons to identify the patients. Patients receiving a prescription for oseltamivir within one day of influenza diagnosis were compared with patients who received no antiviral therapy. The database revealed 7,914 children who received oseltamivir and a control group of 7,914 age-matched and disease severity-matched children who received no antiviral treatment.

The oseltamivir-treated patients had a 52% reduction in the risk of pneumonia compared with children who received no antiviral therapy. Children one to two years of age and those aged six to 12 years experienced the most significant reductions in the risk of contracting pneumonia (52% and 57%, respectively).

The reduction in pneumonia risk for children three to five years of age was not significant (37%). Furthermore, children who were given oseltamivir had a significant 39% decrease in the risk of developing otitis media (middle ear) infection as a complication following influenza.

The children treated with oseltamivir also had a 43% reduction in hospitalizations for pneumonia, a positive trend that did not reach statistical significance. However, hospitalization for respiratory illnesses from any cause fell significantly, by 91%.

Quadrivalent Human Papilloma Virus Vaccine Safe for Children and Adolescents

Speaker: Alex Ferenczy, MD, Professor of Pathology and Obstetrics and Gynecology, McGill University, and Director of Gynecologic Pathology/Cytology, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada

Prophylactic administration of a quadrivalent HPV types 6, 11, 16, and 18 L1 virus-like-particle vaccine (Gardasil, Merck) was found to be generally safe and well tolerated among children nine to 16 years of age. Earlier studies had shown that quadrivalent HPV vaccine in females 15 to 26 years of age was 100% effective in preventing HPV-6/11- and HPV-16/18-related precancerous lesions and genital warts.

An assessment was performed to evaluate the vaccine in females nine to 26 years of age and in males nine to 15 years of age who had been entered in seven clinical trials and who had been randomly selected to receive treatment with either quadrivalent HPV vaccine (11,813 participants) or placebo (9,701 participants) at one, two, and six months. In all seven clinical trials, safety was evaluated via vaccination report card-aided surveillance for 14 days after each injection of HPV vaccine or placebo. Values recorded included serious and non-serious ADEs, temperature levels, injection-site side effects, and systemic clinical adverse experiences.

The proportion of individuals among the safety population who reported an adverse experience was slightly higher in

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those who received HPV vaccine (89.9%) than in those given placebo (85.5%). Among live births, the proportion of infants in whom a medical condition was uncovered was found to be somewhat higher in women who received HPV vaccine than in those who received placebo. Of particular importance, however, the proportions of pregnancies with known outcomes that resulted in a normal infant were comparable between the two study groups: 50% (56/112) in the women given HPV vaccine and 51.3% (59/115) in those receiving placebo.

Overall, the administration of HPV vaccine was generally well tolerated among patients nine to 26 years of age. Its use was associated with an increase in side effects at the injection site and a modest increase in transient low-grade fevers, compared with placebo, all of which were of mild intensity.

Micafungin Effective Against Invasive Candidiasis in Pediatric Patients

Speaker: Antonio Carlos Arrieta, MD, Associate Director and Director of Clinical Research, Division of Pediatric Infectious Diseases, Children's Hospital of Orange County, Orange, California, and Spokesperson for the Micafungin Invasive Candidiasis Study Group

Micafungin (Mycamine, Astellas), an echinocandin agent whose antifungal spectrum includes *Candida* species, was observed to be effective against invasive candidiasis in children. Treatment success rates were similar to those seen with liposomal amphotericin B (AmBisome, Fujisawa).

In the largest pediatric study of its kind to date, 106 children, ranging in age from premature infants to 15-year-olds, were enrolled in a multicenter, randomized, double-blind phase 3 study. In a ratio of 1:1, they were randomly given micafungin 2 mg/kg daily or liposomal amphotericin B 3 mg/kg daily. In this study, 98 patients had a positive *Candida* culture from blood or another sterile site (in the modified intent-to-treat population [mITT]). Forty-eight patients were in the micafungin group, and 50 patients were in the liposomal amphotericin B group. The treatment's success was based on clinical and microbiological responses.

Overall, 92% of the children receiving micafungin (n = 44) and 94% of those receiving liposomal amphotericin B (n = 47) had candidemia. More than two thirds of the patients had an infection caused by a non-*albicans* *Candida* species. The most common organisms were *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. lipolytica*.

A total of 72.9% (35/48) of patients treated with micafungin and 76% (38/50) of those given liposomal amphotericin B had successful outcomes, with overlapping 95% confidence intervals noted between the two agents.

When the patients were stratified by age groups, treatment success rates remained comparable, as follows:

- With micafungin treatment, success rates were 80.8% in children younger than two years of age, 70% in premature babies, and 63.5% in the two- to 15-year-old age group.
- With liposomal amphotericin B, success rates were 77.4% in children below two years of age, 66.7% in premature babies, and 73.7% in those children who were two to 15 years of age. ■