Telithromycin Preferred for Acute Maxillary Sinusitis

Speaker: Itzhak Brook, MD, MSc, Professor, Department of Pediatrics, Georgetown University School of Medicine, Washington, DC

The ketolide telithromycin (Ketek, Sanofi Aventis) has been found to be more effective than the macrolide azithromycin (Zithromax, Pfizer) in eradicating *Streptococcus pneumoniae* from the nasopharynges of patients with acute maxillary sinusitis. Furthermore, the emergence of antimicrobial resistance following therapy occurs only with azithromycin.

The growing resistance of *S. pneumoniae* to penicillin and macrolides has resulted in the development of a new class of antibiotics—the ketolides. A study designed to compare the efficacy of telithromycin with that of azithromycin enrolled 105 patients with acute maxillary sinusitis. Fifty-nine patients received azithromycin 500 mg once daily for three days, and 46 patients received telithromycin 800 mg once daily for five days. Nasopharyngeal cultures were obtained before therapy and at a follow-up visit 10 to 12 days after antibiotic therapy was initiated.

Prior to therapy, 67 potential pathogens had been recovered in 57 patients; 32 of these patients received telithromycin, and 25 received azithromycin. Overall, there were 31 isolates of *S. pneumoniae*: 14 in the azithromycin patients and 17 in the telithromycin patients.

There were also 13 *Haemophilus influenzae* non-type b pathogens, eight of *Staphylococcus aureus*, and seven of *Moraxella catarrhalis*. A single pathogen was recovered in 46 patients, two pathogens were found in six patients, and three different pathogens were found in three patients. No pathogens were found in 48 patients.

Of the 14 *S. pneumoniae* isolates found before therapy in the azithromycin patients, seven were resistant to penicillin, four were resistant to macrolides, and none were resistant to telithromycin.

Of the 17 *S. pneumoniae* isolates in the telithromycin group, nine were resistant to penicillin, six were resistant to macrolides, and none were resistant to telithromycin.

Following treatment, the number of *S. pneumoniae* isolates in the azithromycin patients was reduced from 14 to eight. Five of these isolates were resistant to azithromycin prior to therapy. By contrast, the number of *S. pneumoniae* isolates in the telithromycin patients was reduced from 17 to one after treatment. No differences were noted in the bacterial eradication rate of all other groups of isolates, all of which were susceptible to both azithromycin and telithromycin.

The development of resistance to the antimicrobial agents used was reported in only five isolates (four of *S. pneumoniae* and one of *H. influenzae*). These resistant isolates were recovered only from patients who had received azithromycin.

Cefprozil Useful in Pediatric Acute Otitis Media

Speaker: Michael E. Pichichero, MD, Professor of Microbiology and Immunology, University of Rochester Medical Center, Rochester, New York

Cefprozil (Cefzil, Bristol-Myers Squibb), a second-genera-
The overall clinical cure rate was 80% (37/46).

Cultures were initially positive in about two thirds of the patients. Initial taps resulted in the growth of beta-lactamase–producing (blac+) *Haemophilus influenzae* (Hi) in 23 children; drug-resistant *Streptococcus pneumoniae* (Spn) grew in 22 children, Hi and Spn grew in four children, *Moraxella catarrhalis* grew in three children, and other pathogens developed in two children. The number of organisms isolated from the children with positive cultures was more than 45 because of multiple organisms isolated in several patients.

Bacteriological eradication on the fourth to sixth days by repeated taps was achieved in 78% (39/50) of the children, with three newly emerging infections identified during the antibiotic treatment period. In this group, 13 of 15 penicillin-susceptible pneumococci were eradicated, five of seven penicillin-intermediate pneumococci were eradicated, and 16 of 23 Hi isolates were eradicated, including three of five blac+ Hi and 13 of 18 blac− Hi.

No taps were conducted in five patients who were presumed to have been cured, because no middle-ear fluid was present. Four of the other pathogen isolates were eradicated, and no tap was performed for one isolate.

At four to seven days after the completion of treatment, the rates of clinical cure, including those children with superinfection during treatment, were as follows:

- 91% (20/20 patients) against Hi
- 79% (11/14 patients) against penicillin-susceptible pneumococci
- 80% (3/6 patients) against penicillin-intermediate pneumococci
- 75% (3/4 patients) against other pathogens

The overall clinical cure rate was 80% (37/46).

**New Penem Promising in Uncomplicated Skin and Skin Structure Infections**

**Speaker:** Michael Corrado, MD, Physician of Infectious Diseases and President and Chief Executive Officer, Advanced Biologics, New Hope, Pennsylvania

Faropenem medoxomil (Orapem, Replidyne, Inc.), an investigational oral penem antibiotic with potent activity against *Staphylococcus aureus* and *Streptococcus pyogenes*, proved to be at least as effective as amoxicillin/clavulanate (Augmentin, GlaxoSmithKline) in the treatment of uncomplicated skin and skin structure infections (uSSSIs).

In a pivotal, prospective, double-blind clinical trial, 593 patients with a clinical diagnosis of uSSSI, particularly cellulitis, impetigo, folliculitis, or furuncles, were enrolled from 40 centers in Europe, Israel, and South Africa between January 2001 and January 2002. These patients were randomly assigned to received oral faropenem medoxomil 300 mg twice daily for seven days or oral amoxicillin/clavulanate 625 mg three times daily for seven days.

These patients constituted the intent-to-treat (ITT) and safety populations. Of these patients, 246 receiving faropenem medoxomil and 227 receiving amoxicillin/clavulanate were evaluable for the primary efficacy outcome, and 154 patients receiving faropenem medoxomil and 139 receiving amoxicillin/clavulanate were microbiologically evaluable.

The primary objective of the study was met by showing that faropenem medoxomil was at least as effective as amoxicillin/clavulanate, at the dosages used, for clinical responses at the test-of-cure (TOC) visit at seven to 14 days of therapy. Clinical cure rates at the TOC visit were 91% with faropenem medoxomil and 91.2% with amoxicillin/clavulanate.

Microbiological eradication rates were 91.6% with faropenem medoxomil and 90.6% with amoxicillin/clavulanate. Bacteriological responses were as follows:

- with faropenem medoxomil: 91.4% against *S. aureus*, 100% against *S. pyogenes*
- with amoxicillin/clavulanate: 89.7% against *S. aureus*, 97.7% against *S. pyogenes*

The overall safety of these two agents was similar, although diarrhea and nausea were two to three times higher in the patients receiving amoxicillin/clavulanate. Only five patients in the faropenem medoxomil group and six patients taking amoxicillin/clavulanate left the study prematurely because of an adverse drug effect (ADE). No deaths were reported.

**Iclaprim Valuable Against Serious Complicated SSSI Infections**

**Speaker:** Anton Leighton, MD, Medical Affairs, Arpida AG, Muenchenstein, Switzerland

Iclaprim (Arpida AG), a novel diaminopyrimidine antibiotic, has potent activity against a broad spectrum of gram-positive bacteria such as drug-resistant enterococci and methicillin-resistant *Staphylococcus aureus* (MRSA). It was observed to be as effective, or more so, than the standard of care therapy of vancomycin (Vancocin, Eli Lilly) for the treatment of severe hospital infections arising from infected ulcers, burns, and surgical wounds, otherwise known as complicated skin and skin structure infections (cSSSIs).

A phase 2 study was performed to determine the efficacy of iclaprim in patients with cSSSIs. Ninety-two patients were randomly assigned to receive either iclaprim 0.8 mg/kg or 1.6 mg/kg intravenously (IV) twice daily for 10 days or IV vancomycin 1 g twice a day for 10 days.

The test-of-cure (TOC) rates were 92.9% for low-dose iclaprim, 90.3% for high-dose iclaprim, and 92.9% for vancomycin. The drug was well tolerated in these patients, and no drug-related or severe ADEs were observed. Minor ADEs were of little or no clinical significance; they were infrequent and of mild or moderate intensity.

Eradication rates of gram-positive pathogens were 90% for iclaprim 0.8 mg/kg, 80% for iclaprim 1.6 mg/kg, and 72% for vancomycin. *S. aureus*, as expected, was the most frequent...
gram-positive pathogen. Eradication rates were much higher with iclaprim (72%–80%) than with vancomycin (59%).

At the baseline evaluation, there were five cases of MRSA (in four patients receiving iclaprim 0.8 mg/kg and in one patient receiving vancomycin). At the TOC visit, all MRSA organisms were eradicated in the iclaprim-treated patients.

Based on these results, the U.S. Food and Drug Administration granted iclaprim a fast-track designation because it is being developed to treat potentially life-threatening infections (including those caused by MRSA) and because it may benefit patients who cannot tolerate existing therapies.

**Probiotics Cost-Effective in Preventing Antibiotic-Associated Diarrhea**

**Speaker:** Henry S. Sacks, MD, PhD, Professor of Community Medicine, Medicine, and Biomathematics, Mount Sinai School of Medicine, New York, New York

In hospitalized patients who are starting antibiotic therapy, the simultaneous administration of probiotics such as live, nonpathogenic microorganisms (e.g., *Lactobacillus* or *Saccharomyces*) may prevent antibiotic-associated diarrhea (AAD) and reduce costs, and it probably saves lives.

AAD occurs in up to one third of hospitalized patients. One of the most common types of AAD is caused by *Clostridium difficile*. The incidence of *C. difficile* infection has been increasing recently, and this illness can be fatal.

Because of growing evidence that probiotics might prevent AAD, the investigators performed a computer simulation using estimates from the literature and decision analysis software to determine how much could be saved, in terms of costs and morbidity, by prescribing probiotics.

Base-case estimates and ranges included the probability of AAD when antibiotics were given; estimates were 20% (range, 5%–30%), whereas probiotics prevented AAD at a rate of 63% (48%–74%). In patients with AAD, hospital costs increased by $3,669 per patient, length of stay (LOS) increased by 3.6 days, and mortality from the infection, was reported in 24 patients (67%), and the overall mortality rate in the group was 25% (9 of 36).

With respect to the concerns about toxicity, although 64% of this patient population received combination therapy with aminoglycosides along with colistin, only 14% of the patients experienced any deterioration of renal function, and all of these patients had previous renal failure. No cases of renal failure were seen in patients with normal baseline functions. No neurotoxicity was noted.

**Posaconazole Effective Against Zygomycosis**

**Speaker:** Dimitrios P. Kontoyiannis, MD, ScD, Professor, Section of Infectious Diseases, Department of Internal Medicine, University of Texas M.D. Anderson Cancer Center, Houston, Texas

Posaconazole (Noxafil, Schering-Plough), a novel, extended-spectrum triazole antifungal agent, may offer an attractive oral treatment alternative for patients with zygomycosis who cannot tolerate or do not respond to IV amphotericin B formulations (e.g., Amphotericin B, Bristol-Myers Squibb; Ambisome, Gilead).

A total of 91 patients with either proven (69) or probable (22) zygomycosis caused by immunosuppression, poorly controlled diabetes mellitus, or disruption of the skin or mucosal membranes, were enrolled into a “compassionate-use” study; 48 patients had infection that was refractory to previous antifungal therapy, 10 patients were intolerant of the previous therapy, and 33 patients had infection that was both refractory to and intolerant of the therapy. Treatment with lipid amphotericin B had failed in 85% of these patients.

Posaconazole was administered in divided doses of 400 mg twice daily or 200 mg four times a day either orally or enterally with meals and/or nutritional supplements.

In July 2004, questionnaires were sent to investigators who were then treating or who had previously treated patients with zygomycosis under the compassionate-use protocol. Overall, patients received the antifungal agent from August 31, 2001, through November 29, 2004; thus, some patients were receiving ongoing therapy at the time the questionnaires were completed.

The primary efficacy variable—clinical response—was evaluated at the test-of-cure (TOC) point of 12 weeks or earlier after the initiation of posaconazole therapy.
The success rate with posaconazole among patients with zygomycosis refractory to or intolerant to amphotericin B therapy was high (60% at 12 weeks). Of the 91 patients evaluated, 13 had a complete response and 42 had a partial response. An additional 21% had stable disease at week 12. Success was similar when findings were stratified by site of infection, predisposing conditions, the reason for enrollment, or the infecting *Zygomycetes* species. These results compared favorably with patients who tolerated amphotericin B agents. For these patients, the rate of survival was 61% with amphotericin deoxycholate and 69% with its lipid formulations. (Conventional amphotericin B is supplied in combination with sodium deoxycholate for IV administration; hence, it is referred to as amphotericin B deoxycholate.)

**Valacyclovir Beneficial Against Infectious Mononucleosis**

**Speaker:** Henry Balfour, MD, Professor of Pediatrics and Professor of Laboratory Medicine and Pathology, Division of Infectious Diseases, University of Minnesota School of Medicine; and Laboratory Director, University of Minnesota Fairview Virology Laboratory, Minneapolis, Minnesota

Valacyclovir (Valtrex, GlaxoSmithKline), a well-known antiviral agent indicated for the treatment of herpes zoster and genital herpes, has been found to be beneficial for young adults with infectious mononucleosis (IM) and may help to reduce person-to-person spread. Because antiviral therapy has not been effective against Epstein–Barr virus (EBV), the causative agent of IM, a randomized controlled study with valacyclovir was conducted to reassess antiviral therapy for IM.

Twenty students with IM volunteered during the first week of a laboratory-confirmed diagnosis of primary EBV infection. The students were randomly assigned to receive valacyclovir 3 g/day for 14 days; the controls did not receive any antiviral agents. The volunteers visited the clinic about eight times over a period of six months. Patients were examined, their symptoms were evaluated, and specimens were collected for viral analysis at each visit.

Results showed that the severity of IM was significantly lessened by valacyclovir. The proportion of patients with a decrease of 2 log₁₀ quantity of EBV in oral washes from study days 1 to 14 (the primary endpoint) was 7 of 10 (70%) in the valacyclovir group and 1 of 10 (10%) in controls. A clinical benefit was also documented: illness severity scores were significantly lower in the valacyclovir patients than in the controls.

Because the students who received valacyclovir had a significantly reduced quantity of EBV in their saliva and throat cells compared with the controls, it is possible that this antiviral agent might be used to treat IM and to limit person-to-person spread. Relatively few persons were studied; therefore, these results need to be confirmed by testing more patients. The amounts of EBV in the mouth increased after therapy ended, suggesting that a longer period of treatment or the use of an antiviral agent that stays in the body longer might have an even greater benefit.

**Trizivir/Viread Combination Valuable in Antiretroviral Therapy–Naïve Patients with HIV Infection**

**Speaker:** Calvin Cohen, MD, MS, Research Director, Community Research Initiative and Clinical Instructor, Harvard Medical School, Boston, Massachusetts

Because of its efficacy as antiretroviral therapy (ART) and its improved fasting lipid parameters, the nucleoside analogue combination of abacavir, lamivudine, and zidovudine (TZV, Trizivir, GlaxoSmithKline) plus tenofovir disoproxil fumarate (TDF, Viread, Gilead Sciences) once daily may be useful as a protease inhibitor (PI) and non-nucleoside reverse transcriptase (NNRTI)-sparring regimen in patients with human immunodeficiency virus infection (HIV) who are ART-naïve.

Data suggest that zidovudine has increased activity against HIV by incorporating the H65R gene. A zidovudine-containing regimen composed of TZV and TDF, therefore, might be able to provide a greater genetic barrier to resistance and also be a more potent treatment.

To evaluate the safety and efficacy of using three-tablet, once-daily TZV/TDF therapy over 48 weeks, 123 ART-naïve patients with a viral load of HIV-1 RNA of 30,000 copies/ml or greater at the study’s entry received the drug combination once daily.

The primary endpoints included the percentage of patients with HIV-1 RNA below 50 copies/ml at week 48 and the percentage of patients with grade 3 or 4 ADEs and laboratory toxicities. Other endpoints included the percentage of individuals with HIV-1 RNA below 400 copies/ml; CD+ lymphocyte responses; fasting lipid levels; development of phenotypic and genotypic resistance in nonresponders; and changes from baseline fat distribution, bone density, and mitochondrial DNA.

In these ART-naïve patients, TZV/TDF once daily provided virological suppression for those who continued therapy. At 48 weeks, the virological response rates for the intent-to-treat population (ITT) was 41% with fewer than 50 copies/ml and 50% with fewer than 400 copies/ml. The rates were low because of the high rate of premature discontinuation of the study.

Unlike the poor virological response documentation in previous studies that used abacavir and TDF, only 11% of patients withdrew from the study because of virological nonresponse. Of particular interest, TZV/TDF had a favorable effect on fasting lipid parameters, suggesting a synergistic effect. Further study with a longer follow-up period is needed.

In a subset of patients studied, neither lipoatrophy nor bone loss was observed.