Single-Dose Azithromycin Microsphere Formulation for Acute Exacerbation of Chronic Bronchitis

**Speaker:** Marcus J. Zervos, MD, Infectious Diseases Specialist, William Beaumont Hospital, Royal Oak, Michigan, and Wayne State University School of Medicine, Detroit, Michigan

A single dose of a novel formulation of azithromycin microspheres (Pfizer) has proved to be as effective as a seven-day course of levofloxacin (Levaquin®, Ortho-McNeil) for the treatment of an acute exacerbation of chronic bronchitis (AECB). This advance has made it possible to administer an entire regimen as a single oral dose while maintaining tolerability and efficacy.

In a multicenter, randomized, double-blind, double-dummy clinical trial, 551 patients with AECB were randomly assigned to receive azithromycin microspheres as a 2-g single dose or levofloxacin 500 mg once daily for seven days. The primary and secondary endpoints were clinical and bacteriological responses, respectively, in patients with a baseline pathogen at the test-of-cure (TOC) visit between days 14 and 21.

A total of 438 patients—220 receiving azithromycin microspheres and 218 receiving levofloxacin—met the criteria for the clinical-per-protocol (CPP) population at the TOC visit. The CPP cure rates were comparable in the two treatment groups: 93.6% for azithromycin microspheres and 92.7% for levofloxacin.

The bacteriological-per-protocol (BPP) population consisted of 247 patients: 123 received azithromycin microspheres and 124 received levofloxacin. The overall bacteriological eradication rates at the TOC visit were 91.9% for azithromycin microspheres and 94.4% for levofloxacin.

Because many patients were unable to produce sputum at the TOC visit, most of the pathogens were assigned a bacteriological response of presumed eradication according to an assessment of the clinical response. The clinical cure rates for patients with Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, isolated at baseline, were similar in the azithromycin patients (95.0%, 94.7%, and 92.0%, respectively) and in the levofloxacin patients (100%, 90.5%, and 81.3%, respectively).

Both drugs were well tolerated. Because azithromycin therapy can be administered as a single dose, the rate of compliance was 100% in patients following this regimen. In contrast, 14 of 279 patients in the original levofloxacin group (5%) did not complete the entire seven-day course of active treatment.

Moxifloxacin Once-Daily Regimen for Complicated Intra-abdominal Infections

**Speaker:** Mark A. Malangoni, MD, Chairperson, Department of Surgery, MetroHealth Medical Center and Professor of Surgery and Vice President, Department of Surgery, Case Western Reserve University School of Medicine, Cleveland, Ohio

Sequential intravenous (IV)/oral (PO) monotherapy with moxifloxacin HCl (Avelox®, Bayer) once daily for complicated intra-abdominal infections was as effective as IV piperacillin-tazobactam (Zosyn®, Wyeth) four times daily, followed by oral amoxicillin–clavulanate (Augmentin®, GlaxoSmithKline) twice daily, a widely used therapy for this type of infection.

A total of 681 patients were enrolled into a prospective, double-blind, phase 3 trial. Of these, 656 patients were included in the safety population (328 receiving moxifloxacin and 328 receiving comparator therapy), and 379 patients were included in the efficacy population (182 receiving moxifloxacin and 197...
receiving comparator therapy).

After the patients were ranked according to disease severity, they were randomly assigned to receive IV followed by oral moxifloxacin 400 mg every 24 hours or IV piperacillin–tazobactam 3.0/0.375 g every six hours followed by oral amoxicillin–clavulanate 800 mg/114 mg every 12 hours for five to 14 days. Clinical cure and bacteriological eradication rates were recorded at the test-of-cure visit at 25 to 50 days after therapy.

In the patients who were evaluable for efficacy, clinical cure rates were similar for moxifloxacin (79.7%) and comparator therapy (78.2%), as were bacteriological eradication rates, at 77.9% and 77.4%, respectively. Higher clinical cure rates were recorded in the moxifloxacin patients (85.4%) than in the patients receiving comparator therapy (72%) when the infection was acquired in a hospital.

Higher cure rates were also observed with moxifloxacin (85.4%) than with comparator therapy (72.3%) in infections caused by Bacillus fragilis. Outcomes were similar in the two treatment groups in patients with intra-abdominal abscesses, community-acquired infections, and infections caused by Escherichia coli.

Adverse drug events (ADEs) were similar in both groups. The three most common ADEs were diarrhea, nausea, and elevated gamma glutamyl transferase levels.

Reduced Risk of Pneumonia in Influenza Patients Treated with Oseltamivir
Speaker: Beth L. Nordstrom, PhD, Epidemiologist, Ingenix Epidemiology, Aburndale, Massachusetts

In a large population of patients with influenza, treatment with oseltamivir (Tamiflu®, Hoffman-LaRoche Ltd.) was associated with a significant reduction in the risk of pneumonia. Several clinical studies showed that oseltamivir was up to 92% effective in preventing influenza in adolescents, adults, and elderly adults when it was taken once daily for seven days. These studies suggested that the risk of pneumonia and other sequelae of influenza might be decreased in patients who used this agent.

To determine the risk of pneumonia, the frequency of antibiotic dispensing, and hospitalization rates among influenza patients in a real-world setting, investigators conducted a retrospective cohort study using medical and prescription claims data for members of United Healthcare, a large U.S. health insurer, and a source population from the Ingenix Research Database. The cohort included patients one year of age or older with an insurance claim diagnosis of influenza between December 1, 1999, and March 31, 2002, and who either had taken oseltamivir or who had not taken any antiviral medication. The researchers also assessed the rate of dispensing of antibiotics or hospitalization within 30 days after an influenza diagnosis. Separate analyses were performed, according to the number of outcomes (exposed vs. unexposed) in patients receiving oseltamivir and in patients who had not taken oseltamivir, across three age ranges, as shown in the chart in the next column.

In the 13- to 59-year-olds, the risk of pneumonia was reduced by 19%; in fact, the decreased risk was most dramatic in the youngest and oldest age groups. In the patients aged one to 12 years, the risk was reduced by 66%. In patients 60 years of age and older, the risk was reduced by 59%. Finally, in these two age groups, the incidence of required antibiotic therapy and hospitalization was also decreased.

Anidulafungin in HIV-Negative Patients with Esophageal Candidiasis
Speaker: Jennifer A. Schranz, MD, Director, Clinical Research, Vicuron Pharmaceuticals, King of Prussia, Pennsylvania

Anidulafungin (Vicuron Pharmaceuticals), a novel echinocandin antifungal antibiotic with potent in vitro and in vivo activity against Candida species, including azole-resistant and camphoterin B-resistant organisms, was as effective and as well tolerated as fluconazole (Diflucan®, Pfizer) in HIV-negative patients with esophageal candidiasis. This therapy gives physicians one more option for patients with fluconazole intolerance as well as a benefit of no dose adjustments required for patients with renal or hepatic impairment or for those taking concomitant medications.

Initially, a phase 3, randomized, double-blind, double-dummy comparative trial was conducted from April 2001 through October 2002 from sites in South Africa, Thailand, Argentina, and the U.S. to compare the efficacy and safety of anidulafungin versus fluconazole in patients with esophageal candidiasis. Of 601 patients, 300 were assigned to receive anidulafungin 100 mg IV on the first day and 50 mg IV daily, and 301 were to receive fluconazole 100 mg orally each day. Treatment lasted for 14 to 21 days for patients who remained symptom-free for seven days.

The primary method of efficacy analysis was a comparison of endoscopic response in evaluable per-protocol patients at the end of therapy (EOT). Secondary efficacy analyses included (1) the clinical response (a successful response was the absence or improvement of symptoms compared with baseline values) and (2) the mycological response (a successful response was proven or presumed eradication of baseline Candida species).

Of the patients who agreed to HIV testing, 114 of 136 patients in the anidulafungin group (83.6%) and 123 of 143 in the fluconazole group (86.9%) were HIV-positive. At the EOT for the overall study, the endoscopic success rate was 97.2% with anidulafungin (242 of 249 patients) and 98.8% (252 of 255 patients) with fluconazole. Anidulafungin was found to be statistically non-inferior to fluconazole. High rates of microbiological success were also seen for anidulafungin (86.7%) and fluconazole (90.9%).

For the documented HIV-negative subgroup from the large clinical trial, 19 anidulafungin patients and 18 fluconazole patients were in the clinically evaluable EOT population. Fungal infections in those patients were caused by immunosuppression resulting from cytotoxic therapy for cancer or...
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preventing transplanted organ rejection; the overuse of antibiotics; the excessive use of corticosteroids; or invasive surgical techniques in high-risk individuals. Most of these patients had moderate-to-severe symptoms of disease.

At the EOT, the clinical response rate and the endoscopic success rate were 100% for both anidulafungin and fluconazole treatment groups of patients. The mycological response rates in the EOT population were 81.8% (9 of 11 patients) taking anidulafungin and 90.9% (10 of 11 patients) taking fluconazole.

**Early Treatment with Enfuvirtide Found to Be Most Beneficial**

**Speaker:** Calvin J. Cohen, MD, Research Director, Community Research Initiative of New England and Clinical Instructor, Harvard Medical School, Boston, Massachusetts

The early use of enfuvirtide (Fuzeon®, Roche/Trimeris) with an optimized-background (OB) regimen in treatment-experienced HIV-infected patients results in better outcomes, including significantly lower virological failure rates and markedly less loss of active background agents, when compared with regimens that do not contain enfuvirtide; it also preserves future drug options.

These findings were derived from a new analysis of the TORO (T-20 [Fuzeon®] vs. Optimized Regimen Only) studies, two randomized phase 3 clinical trials that assessed the efficacy and safety of enfuvirtide plus an OB regimen of antiretroviral agents (ARVs) versus an OB regimen alone in 995 triple-class experienced HIV-infected patients.

The patients were randomly assigned, in a 2:1 fashion; 661 received enfuvirtide plus an OB regimen and 334 received an OB regimen alone. The analysis was designed to explore the development of resistance and antiretroviral efficacy of initial or subsequent regimens in treatment with and without enfuvirtide.

Results from these exploratory and retrospective analyses of the TORO studies indicated that 33% of patients who did not receive enfuvirtide in their regimen at the beginning of the TORO trials developed resistance to at least one active therapeutic option. In contrast, only 13% of those who began their treatment with an enfuvirtide-based regimen at the initiation of the TORO studies experienced a loss of at least one active treatment option after 48 weeks because of virological failure.

In addition, 32% of the patients receiving an enfuvirtide-based regimen from the outset of the study achieved undetectable levels of HIV-1 RNA (less than 400 copies/ml) compared with 22% of the patients receiving a non–enfuvirtide-based regimen. This finding represents a significant difference favoring the use of an enfuvirtide-based regimen.

**Tipranavir-Based Regimen Valuable in Treatment-Experienced Patients with HIV Infection**

**Speaker:** Charles Hicks, MD, Associate Professor of Medicine, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina

Tipranavir (TPV) (Boehringer Ingelheim), a novel nonpeptidic protease inhibitor (PI), now in late phase 3 clinical development, plus low-dose ritonavir (r) (Norvir®, Abbott) was found to be significantly superior to currently available comparator protease inhibitors (CPIs) boosted by ritonavir (CPI/r). After 24 weeks of treatment, the virus was suppressed in patients with advanced HIV disease who had been exposed to more than three antiretroviral agents.

The researchers arrived at this conclusion from an interim analysis of the RESIST-1 (Randomized Evaluation of Strategic Intervention in Multidrug-Resistant Patients with Tipranavir) study. This study, a randomized, controlled, open-label, phase 3 clinical trial conducted in the U.S., Canada, and Australia, was designed to evaluate the safety and efficacy of tipranavir boosted with low-dose ritonavir versus a low-dose ritonavir-boosted CPI in treatment-experienced patients with documented PI resistance.

A total of 620 patients were randomly assigned to TPV/r 500 mg/200 mg or CPIs combined with ritonavir at its standard boosting dose. The CPIs included lopinavir (Kaletra®, Abbott), saquinavir (Fortovase®, Roche), amprenavir (Agenerase®, GlaxoSmithKline), and indinavir (Crixivan®, Merck).

All of the patients combined their PIs with an optimized-background (OB) regimen of antiretroviral agents. These drugs were selected on the basis of the patients’ treatment history and baseline results of genotypic resistance testing.

At the 24th week, treatment response, defined as a 1 log10 or greater decrease in viral load from the baseline, was achieved in 41.5% of the patients in the TPV/r treatment group and in 22.3% of patients in the CPI/r arm. Furthermore, a greater proportion of patients taking TPV/r achieved a viral load below the levels of quantification (defined as less than 400 copies/ml and less than 50 copies/ml) compared with those who received CPI/r. A total of 34.7% of TPV/r-treated patients and 16.5% of the CPI/r patients achieved viral loads of less than 400 copies/ml; 25.1% of the TPV/r patients achieved less than 50 copies/ml, compared with 10% of patients receiving CPI/r-based therapy.

Patients taking TPV/r experienced greater increases in their CD4+ cell counts (+36 cells/mm3) than did those taking a CPI/r (+6 cells/mm3).

**Four-NRTI Second-Line Regimen for Early Virological Failure**

**Speaker:** Allan E. Rodriguez, MD, Associate Professor of Medicine, Division of Infectious Diseases, University of Miami School of Medicine, Miami, Florida

A single-class quadruple therapy of nucleoside reverse transcriptase inhibitors (NRTIs), consisting of a fixed-dose combination of abacavir, lamivudine, and zidovudine (Trizivir®, GlaxoSmithKline) plus tenofovir disoproxil fumarate (TDF) (Viread®, Gilead) may become the treatment of choice for HIV-infected patients who are experiencing early virological failure with highly active antiretroviral therapy (HAART), composed of two NRTIs plus a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.

Fifty-one patients with HIV infection who were experiencing early virological failure on a regimen of zidovudine (Retrovir®, GlaxoSmithKline) or stavudine (d4T) (Zerit®, Bristol-Myers Squibb) plus lamivudine (3TC) (Epivir®, GlaxoSmithKline), combined with either a PI or an NNRTI, were switched to open-
Lopinavir/Ritonavir plus Efavirenz Offers NRTI-Sparing Regimen in HIV Infection  
**Speaker:** Francois Raffi, MD, Professor, Infectious Diseases Department, University Hospital, Nantes, France

Final results of a 48-week pilot study indicated the soundness of the following concept: a nucleoside reverse transcriptase (NRTI)—sparing regimen of lopinavir/ritonavir (LPV/r) (Kaletra®, Abbott) and efavirenz (EFV) (Sustiva®, DuPont), a protease inhibitor (PI) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). Both of these drugs are potent preferred agents in their respective classes. This regimen provides a safe, well-tolerated, and effective treatment approach and avoids the cross-resistance seen between drugs in the same class and mitochondrial toxicity problems associated with NRTIs.

Eighty-six patients with HIV infection were enrolled into the BIKS (Bithrapy of Kaletra and Sustiva) study, a pilot, multicenter, open-label trial. Of the 86 patients, 65 were antiretroviral (ARV)-naive and 21 were ARV-experienced but NNRTI-naive. The study was designed to evaluate the safety and immunological and virological activity of dual-therapy LPV/r 533/133 mg twice daily and EFV 600 mg once daily in patients with HIV infection.

It should be noted that dose adaptation is required for patients taking this two-agent combination. The LPV/r dose should be increased by one third because of an induction of lopinavir metabolism by EFV, which reduces the lopinavir area-under-the-curve (AUC) concentration by 40%.

The baseline mean HIV RNA level was 4.8 log10 copies/ml, and the mean CD4 cell count was 307/mm³.

The duration of the study was 48 weeks, with a 24-week extension and follow-up at day 0 (zero) and at weeks 4, 8, 16, 24, 36, and 48.

At 48 weeks, 65 patients were evaluable, with 21 patients having discontinued the study. In this latter group, only one patient in the ARV-naive group had experienced virological failure, at week 24. The remaining discontinuations were a result of patients being lost to follow-up and emerging ADEs. A high proportion of patients who remained in the study to its conclusion achieved virological success.

At 24 weeks, a mean HIV RNA level below 400 copies/ml was reported in 93% of the active-treatment population (67 of 72 patients) and in 78% of the intent-to-treat population (67 of 86 patients).

At 48 weeks, a mean HIV RNA level of less than 50 copies/ml was observed in 91% of the active-treatment population (59 of 65 patients) and in 69% of the ITT population (59 of 86 patients). Overall, virological failure was documented in four patients, three of whom had been noncompliant with their medications.

Among patients with a detectable plasma viral load at the 24th or 28th week, genotypic testing showed an absence of PI resistance mutations and two cases of emergence of k13N resistance.

**Peginterferon alfa-2a plus Ribavirin in Patients with HIV and HCV Co-infection**  
**Speaker:** Douglas T. Dieterich, MD, Vice Chair and Chief Medical Officer, Department of Medicine, and Professor of Medicine, Mount Sinai Medical Center, New York, New York

Patients who are co-infected with HIV and hepatitis C virus (HCV) who achieve a sustained virological response with peginterferon alfa-2a (Pegasys®, Roche) and ribavirin (Rebetol®, Schering) combination therapy have a much improved health-related quality of life (HRQL) compared with co-infected patients who remain HCV-positive.

An analysis of data from APRICOT (the AIDS Pegasys Ribavirin International Co-Infection Trial), a pivotal study that evaluated the safety and efficacy of pegylated interferon/ribavirin combination therapy in 860 co-infected patients, was performed to measure the differences in HRQL in responders versus nonresponders. Initially, these patients were randomly treated with 48 weeks of peginterferon alfa-2a 180 mg weekly plus ribavirin 800 mg/day or with standard interferon plus ribavirin.

Overall, 40% of patients taking the peginterferon alfa-2a plus ribavirin combination therapy achieved a sustained virological response, which represents a significant positive difference in favor of this therapy versus the comparator group ($P < .0001$).

At the end of 72 weeks of follow-up, patients who received peginterferon alfa-2a plus ribavirin and who achieved a sustained virological response had a better HRQL than nonresponders on seven of eight domains, as measured by the Short Form 36-item (SF-36) Health Survey and the Fatigue Severity Scale. These domains included physical functioning, social functioning, physical role, general health, mental health, pain index, and vitality. Differences in vitality, general health, Fatigue Severity Scale scores, and Visual Analog Scale scores were statistically and clinically significant.