Once-Daily Short-Duration Antimicrobial Therapy for Community-Acquired Pneumonia

Speaker: John Pullman, MD, Infectious Diseases Specialist, Internal Medicine, Mercury Medical Center, Butte, Montana.

Telithromycin (Ketek™, Aventis), administered once daily for five to ten days to patients with CAP, has been found to be as effective and safe as standard twice-daily, 10-day treatment with clarithromycin (Biaxin®, Abbott), a commonly prescribed macrolide; this suggests that in an environment of increasing macrolide resistance, telithromycin might be an effective alternative for the treatment of patients with CAP.

Data were analyzed from two phase III, multicenter, actively controlled, randomized, double-blind trials of telithromycin versus clarithromycin for the treatment of CAP in 1,023 patients, focusing on antibacterial activity against Streptococcus pneumoniae, particularly erythromycin-resistant strains. In the first study, 448 patients received either oral telithromycin 800 mg once daily or oral clarithromycin 500 mg twice daily for 10 days. In the second study, 575 patients received either telithromycin 800 mg once daily for 5 days, telithromycin 800 mg once daily for 7 days, or clarithromycin 500 mg twice daily for 10 days.

In S. pneumoniae–associated (either single-pathogen or mixed-pathogen) infections, telithromycin was clinically and bacteriologically effective in 97.7% of patients; clarithromycin was effective in only 75%. In addition, telithromycin was active in 88.9% of patients with erythromycin-resistant S. pneumoniae; clarithromycin was active in only 75%.

Once-Daily Antitherpetic Agent for Suppression of Genital Herpes

Speaker: Lawrence Corey, MD, Professor of Medicine and Laboratory Medicine, and Head, Virology Division, University of Washington; and Head of the Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, Washington.

A daily dose of valacyclovir as suppressive therapy has been shown to reduce the transmission of symptomatic genital herpes by 77% in healthy heterosexual monogamous couples. Overall, 1,484 couples were randomly assigned in a double-blind study and were included in the intent-to-treat population. The herpes simplex virus-2 (HSV-2)—seropositive source partners with a history of fewer than 10 episodes per year were randomly assigned, in a 1:1 ratio, to receive valacyclovir 500 mg once daily or placebo for eight months. The HSV-2 seronegative-susceptible partners were monitored monthly for clinical or subclinical (serological) acquisition of genital herpes. All couples were provided with condoms and were counseled on safer sexual behavior at all study visits.

The primary endpoint was the proportion of susceptible partners with a first episode of symptomatic genital herpes, confirmed by HSV-2 culture, polymerase chain reaction (PCR), or seroconversion. The secondary endpoint was the presence of genital HSV-2 in the susceptible partners. A total of 741 source partners received placebo, and 743 received valacyclovir. In total, 488 susceptible partners were women and 996 were men.

The study showed that once-daily suppressive therapy with valacyclovir reduced the transmission of symptomatic genital herpes by 77% compared with placebo. Seventeen subjects (2.3%) in the placebo group and four (0.5%) in the valacyclovir group acquired symptomatic genital herpes.

In addition, suppressive antitherpetic therapy decreased laboratory-confirmed genital herpes and/or seroconversion in partners who did not develop active cases of the disease by...
50%, compared with those taking placebo. Twenty-eight subjects (3.8%) in the placebo group and 14 (1.9%) of those in the valganciclovir group acquired HSV-2 infection. The reported frequency of sexual activity was similar in both groups.

**New Prophylactic Antifungal Agent for Patients Undergoing Hematopoietic Stem Cell Transplantation**

**Speaker:** Jo-Anne van Burik, MD, Assistant Professor of Medicine, Division of Infectious Diseases, Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

Mycangin (Fujisawa Healthcare, Inc.), a member of a new class of antifungal agents known as the echinocandins, has demonstrated a greater overall success rate than fluconazole (Diflucan®, Pfizer) as antifungal prophylactic therapy and has a more positive safety profile when administered to patients undergoing hematopoietic stem cell transplantation (HSCT) during the neutropenic phase.

A multicenter, randomized, double-blind phase III study was carried out in the United States and Canada involving 882 patients with HSCT who were older than six months of age. The patients were randomly assigned to receive micafungin 50 mg (1 mg/kg if their body weight was below 50 kg) or fluconazole 400 mg (8 mg/kg if their body weight was below 50 kg) daily.

Treatment was begun within 48 hours of conditioning with HSCT and was continued for up to five days following an increase of more than 500 cells/mm² in neutrophils, development of a fungal infection, unacceptable toxicity, death, or more than 42 days following HSCT. Treatment success was defined as the absence of fungal infection through four weeks after therapy. The median duration of treatment was approximately 18 days in both treatment groups.

The overall success rate was significantly higher for patients receiving micafungin (80%) than for those receiving fluconazole (73.5%). Micafungin was associated with a consistently higher treatment success rate across all subgroups. Fewer patients in the micafungin group acquired aspergillosis compared with those in the fluconazole group (0.2% vs. 1.5%), and fewer patients taking micafungin required empirical antifungal therapy compared with patients taking fluconazole (15.1% vs. 21.4%). Both drugs were effective in preventing candidiasis (0.9% vs. 0.4%), and micafungin was more effective in preventing Fusarium infections (0.9% vs. 2.0%).

The safety profile for the micafungin group was more positive than that for the fluconazole group. Both treatment groups experienced a comparable number of adverse events (15.1% in the micafungin group and 16.8% in the fluconazole group), but significantly fewer micafungin-treated patients withdrew from the study as a result of drug-related adverse events compared with those taking fluconazole (4.2% vs. 7.2%).

**Meeting Highlights: Antimicrobial Agents and Chemotherapy**

**Prophylaxis of Cytomegalovirus Infection in Solid-Organ Transplant Recipients**

**Speaker:** Carlos V. Paya, MD, Professor of Medicine and Immunology, Infectious Diseases Division, Mayo Clinic, Rochester, Minnesota.

On the basis of predefined guidelines, new data from a phase III clinical trial have successfully demonstrated that oral valganciclovir (ValcyteTM, Roche) for the prevention of CMV infection in solid-organ transplant recipients. Additional benefits include a once-daily dosing schedule, better viral suppression during treatment, and an absence of ganciclovir-related genotypic resistance.

A total of 364 CMV-negative patients who had received a solid-organ transplant from CMV-positive donors were stratified by organ type (177, liver; 120, kidney; 11, kidney-pancreas; and 56, heart). These recipients were then randomly assigned, in a 1:1 ratio of valganciclovir to ganciclovir, to receive valganciclovir 900 mg once daily or oral ganciclovir 1,000 mg three times daily. Treatment was initiated within 10 days after transplantation and continued for 100 days, with follow-up extending to six months.

The study showed a low incidence of CMV disease (syndrome tissue-invasive) during the first six months of treatment, at rates of 12.1% (29/239) with valganciclovir and 15.2% (19/27) with ganciclovir at six months. Only four overt cases in each therapy arm occurred during the treatment period.

Valganciclovir demonstrated several beneficial aspects not apparent in patients receiving ganciclovir. For instance, it conferred better viral suppression during treatment than did ganciclovir; the rates of measurable viral load (more than 400 copies per milliliter) were 25% in patients taking valganciclovir and 10.4% in patients taking ganciclovir. The rate of viremia, however, was comparable in the two treatment groups at six months after transplantation.

Acute rejection was observed less frequently in patients taking valganciclovir (29.7%) than in those taking ganciclovir (36%) for all three types of organs treated. In addition, no ganciclovir-resistant strains were associated with valganciclovir prophylaxis, whereas a rate of 2% was observed with ganciclovir.

Both drugs were well tolerated, with low rates of withdrawal resulting from adverse events. Because valganciclovir is the prodrug of ganciclovir, drug-related adverse events were similar in the two drugs.

**Alcohol-Based Gels for Hospital Infection Control**

**Speaker:** Maureen Schultz, Infection Control Specialist, Veterans Affairs Medical Center, Washington, DC.

Although standard hygiene guidelines for hospital personnel include regular hand-washing to prevent disease transmission between patient examinations, new alcohol-based hand sensitizers may offer a more effective approach for reducing dangerous nosocomial infections caused by resistant bacteria.

Rates of new nosocomial cases of vancomycin-resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), and Clostridium difficile colitis were evaluated before and after hospital-wide distribution of an alcohol-based hand rub (ABHR). Starting in August 2000, ABHR dispensers were installed in all inpatient and clinic rooms as well as in operating rooms and other clinical locations in the VA Medical Center in Washington, DC, a tertiary-care teaching hospital with 167 acute care and 120 long-term hospital beds. No change was made in the availability of hand soap. An educational program was developed to encourage use of the ABHR after each patient contact or after contact with objects in the patient’s room.
Both formal and informal surveys demonstrated widespread acceptance and use of the ABHR. In the three-year period before the ABHR dispensers had been placed, the number of new MRSA nosocomial infections ranged from 78 to 113; two years after placement of the dispensers, the number of cases had fallen to 64. Over a three-year period before ABHR use, the number of cases of VRE infection had ranged from 40 to 42; two years after placement of the dispensers, the number of cases decreased to 20. The same findings were seen with the number of clostrial infections, which decreased from 34 to 26.

Boosted Protease Inhibitor Therapy in Treatment-Experienced, HIV-Infected Patients

**Speaker:** Jan Gerstoft, MD, Senior Consultant, Rigshospitalet, Copenhagen, Denmark.

A 48-week trial on the efficacy and safety data is the first head-to-head study of ritonavir (Novir®, Abbott)-boosted protease inhibitor (PI) therapy in treatment-experienced patients with human immunodeficiency virus (HIV) infection. Results indicated that saquinavir (Fortovase®, Roche)/ritonavir reduced HIV levels to less than 50 copies per milliliter in a greater proportion of treatment-experienced, HIV-infected patients, had a better safety profile, and had a better lipid profile than those taking indinavir (Crixivan®, Merck).

The MaxCmin1 study, an open-label, randomized, phase IV trial, included 317 HIV-positive patients enrolled from 14 countries in North and South America and Europe. The primary objective was to evaluate differences in virological efficacy and toxicity among patients with a clinical need for a ritonavir-boosted PI treatment. Patients received either 1,000 mg of saquinavir (n = 148) or indinavir 800 mg (n = 158), each co-administered with a small 100-mg dose of ritonavir, for 48 weeks. Eleven randomly assigned patients did not initiate therapy.

At 48 weeks, the ritonavir-boosted PI therapies showed enhanced virological and immunological effects in the patients given boosted saquinavir compared with the patients receiving boosted indinavir. Boosted saquinavir reduced HIV ribonucleic acid (RNA) levels below 50 copies per milliliter in 57% of treated patients but in only 46% of those receiving boosted “indinavir,” according to the most stringent “intent-to-treat” analysis, which considered dropouts as failures. Immunologically, the median CD4 cell count increases from baseline were 85 cells/mm³ in the boosted saquinavir treatment arm and 73 cells/mm³ in the boosted indinavir treatment arm.

Boosted saquinavir had a significantly better lipid profile; patients receiving boosted indinavir had markedly greater elevations in lipid levels at 48 weeks than those receiving boosted saquinavir. These findings included increases in fasting total cholesterol (17% vs. 8%), low-density lipoprotein (LDL)-cholesterol (18% vs. 3%), and triglyceride levels (22% vs. 9%).

In addition, more patients withdrew from the study because of treatment-limiting, nonfatal clinical adverse events in the boosted indinavir treatment arm (28%) than in the boosted saquinavir treatment arm (15%). More patients receiving boosted indinavir had at least one grade 3 or 4 adverse event (39%) compared with patients receiving boosted saquinavir (30%).

**Meeting Highlights: Antimicrobial Agents and Chemotherapy**

**Dual Protease Inhibitor Therapy for Antiretroviral-Naive, HIV-Positive Patients**

**Speaker:** Robert L. Murphy, MD, Professor of Medicine, Division of Infectious Diseases, The Feinberg School of Medicine, Northwestern University, Chicago.

A lopinavir/ritonavir-based treatment regimen has been shown to offer considerable long-term activity in antiretroviral (ART)-naive, HIV-infected patients, suppressing HIV to undetectable levels and remaining well tolerated through four years of therapy.

An ongoing phase II study—M97-720—is the first trial to assess the efficacy and safety of lopinavir/ritonavir (Kaletra®, Abbott) in HIV-infected patients and is thus the study with the largest follow-up in patients given this boosted PI. One hundred ART-naive patients were randomly assigned to receive one of three dosages of lopinavir/ritonavir (200/100 mg twice daily, 400/100 mg twice daily, or 400/200 mg twice daily) together with stavudine (d4T) (Zerit®, Bristol-Myers Squibb) 40 mg twice daily and lamivudine (3TC) (Epivir®, GlaxoSmithKline) 150 mg twice daily, given either after three weeks of monotherapy or from entry into the study. After 48 weeks, the therapy for all patients was converted to open-label lopinavir/ritonavir 400/100 mg twice daily plus d4T and 3TC.

Through four years of follow-up of the original study group, 72 patients remained in the study, all achieving undetectable levels of HIV RNA below 400 copies per milliliter; 70 patients demonstrated HIV RNA levels below 50 copies per milliliter according to intent-to-treat analysis. This finding is of considerable importance because undetectability prolongs the development of resistance and leads to long-term treatment success. Indeed, no PI resistance mutations have been observed in those patients with a sustained viral load.

Lopinavir/ritonavir was well tolerated, with only seven patients discontinuing therapy because of drug-related side effects. This is significant because well-tolerated drugs with few adverse effects enhance patients’ adherence to treatment and, at the same time, can improve the patients’ quality of life.

**Nucleotide Reverse Transcriptase Inhibitors in Treatment-Naive, HIV-Positive Patients**

**Speaker:** Joel Gallant, MD, Associate Professor of Medicine, Department of Infectious Disease, Johns Hopkins University School of Medicine, Baltimore.

A tenofovir disoproxil fumarate (TDF) (Viread®, Gilead)-based regimen has proved to be as effective in maintaining undetectable levels of HIV RNA as a stavudine (d4T) (Zerit®, Bristol-Myers Squibb)-based regimen in treatment-naive, HIV-infected patients, while providing more favorable lipid and mitochondrial deoxyribonucleic acid (DNA) profiles with fewer nucleoside-associated adverse effects.

In an ongoing, three-year, multicenter, randomized, double-blind, controlled trial, the efficacy and safety of a regimen of tenofovir DF, lamivudine (3TC), and efavirenz (Sustiva®, DuPont) were compared with the efficacy and safety of a regimen consisting of stavudine, 3TC, and efavirenz in 600 ART-naive, HIV-infected patients. Data through 48 weeks demonstrated statistically significant differences in lipid profiles for the tenofovir DF (n = 199) and stavudine (n = 208) treatment groups.
Meeting Highlights: Antimicrobial Agents and Chemotherapy

Patients receiving tenofovir DF experienced a mean change from a baseline triglyceride level of 12 mg/dl; patients receiving stavudine experienced a significant increase of 84 mg/dl. The increase in total fasting cholesterol levels was significantly lower in patients receiving tenofovir DF than in those receiving stavudine (29 mg/dl vs. 57 mg/dl). The incidence of nucleoside analogue–associated toxicities, such as peripheral neuropathy and lipodystrophy, was 3% in the tenofovir DF arm and 10% in the stavudine-containing arm.

Overall, 87% of patients in both treatment arms achieved HIV RNA levels of less than 400 copies per milliliter, whereas 82% of the tenofovir DF group and 81% of the stavudine group achieved levels of HIV RNA below 50 copies per milliliter. A mean increase from a baseline of 169 and 167 CD4 cells was observed in the tenofovir DF and stavudine study arms.

Notably, a substudy analysis of 227 patients was conducted to explore the effect of treatment on mitochondrial DNA and its potential association with adverse effects. Because infection with HIV appears to result in decreased mitochondrial levels in untreated individuals, levels also were assessed in a control group of 49 uninfected males.

Patients given tenofovir DF experienced a significant median increase from a baseline of 82 copies per cell of mitochondrial DNA, bringing the median level to that seen in the uninfected control group. An increase of only 18 copies per cell of mitochondrial DNA was seen in the patients taking stavudine.

Protease Inhibitors for Patients with Hepatitis C and HIV Co-infection

Speaker: Douglas T. Dieterich, MD, Chief Medical Officer and Vice Chairman, Department of Medicine, Mount Sinai Medical Center, New York.

In an assessment of the use of PI-containing highly active antiretroviral therapy (HAART) in the treatment of HIV-infected patients co-infected with hepatitis C virus (HCV), nelfinavir (Viracept®, Agouron) has been shown to be effective. It is the safest antiretroviral agent among the various PIs evaluated, based on comparisons of grade 3 and grade 4 elevations of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

With the prevalence of HCV/HIV co-infection on the rise, it was decided to study the immunological and virological outcomes in HCV co-infected patients receiving PI therapy for HIV infection. Using a retrospective chart review of 1,052 patients with HCV and HIV co-infection who had received more than three months of PI therapy, a retrospective study analyzed safety data, viral load, CD4 cell count, and treatment history (HIV and HCV). The mean duration of PI-containing HAART therapy in these patients was 39.5 months.

Of the 1,052 patients whose case report forms were reviewed, 77% of the patients were male, with a mean age of 44 years. The mean number of years elapsed since the HIV diagnosis was 8.64. The median baseline CD4 cell count was 240 cells/mm³, and the median viral load was 4.11 log₁₀. Overall, 428 patients received nelfinavir, 364 received indinavir, 182 received saquinavir, 149 patients received ritonavir, and eight received amprenavir. In all, 107 patients were taking dual PIs. The mean duration of PI-inclusive HAART therapy was 39.5 months.

With regard to liver toxicity, 3% of patients taking nelfinavir had grade 3 or 4 elevated AST levels, in contrast to 7% of indinavir-treated patients, 3% of those taking ritonavir, and 7% of those taking saquinavir. Four percent of patients taking nelfinavir had a grade 3 or 4 elevation in ALT levels, compared with 7% of patients taking indinavir, 8% of those taking ritonavir, and 11% of those taking saquinavir.

Throughout the study, patients had a mean CD4 cell count of +118 cells/mm³ and a decrease in viral load of −1.09 log₁₀ with 57% having a viral load of less than 400 copies per milliliter. For the nelfinavir patients at these same baseline CD4 cell counts and viral loads, increases in CD4 counts and decreases in viral load were equivalent to those reported for the total study population.

A Switch from Protease Inhibitors to Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Patients with HIV Infection

Speaker: Thierry Prazuck, Sr., MD, Infectious Diseases Specialist, Centre Hospitalier Regional, Orleans, France.

Switching to the NNRTI nevirapine (Viramune®, Boehringer Ingelheim) or, to a lesser degree, efavirenz (Sustiva®, DuPont) in HIV-infected patients who had been on an effective PI-containing regimen has been shown to result in improved long-term treatment success as well as in the correction of PI-associated lipodystrophy.

To reduce the toxicity and complexity of PI-containing HAART regimens and to improve long-term patient compliance, simpler PI-sparing treatment approaches that contain NNRTIs are being used. In an effort to select between nevirapine and efavirenz as an appropriate substitute for an efficacious PI in an AIDS-related virus (ARV) regimen, as demonstrated by a study carried out. One hundred thirty-nine sequential HIV-positive patients were enrolled. Entry criteria included treatment with a PI-containing regimen for more than one year and an undetectable viral load for six months. In this study group, the PI was substituted with nevirapine in 82 patients and with efavirenz in 57 patients.

Within 24 months after the switch from PI to an NNRTI regimen, 80.3% of patients continued the post-switch regimen and were not in therapeutic failure. The success rates were similar in the patients taking nevirapine and in those taking efavirenz. The NNRTI switch in the more treatment-experienced patients, however, was better in the patients who received nevirapine.

Adverse events leading to discontinuation of therapy were more frequent in the patients receiving efavirenz, and the difference increased after six months of therapy. The PI-associated adverse metabolic changes were partially corrected by the NNRTI switch from PI-containing HAART. This is not surprising, because it is well known that many PIs are associated with lipodystrophy, characterized by increases in LDL-cholesterol (the “bad” cholesterol) and increases in triglycerides. Nevirapine treatment, in contrast, resulted in a trend toward lower total cholesterol levels and in significantly decreased triglyceride levels.