Prevention of Opportunistic Infections

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Dr Benson was invited by the IAS-USA to select the key clinical findings presented or published in the last year on the prevention of opportunistic infections and to provide a commentary on the current status of this treatment area. Dr Benson is Associate Professor of Medicine at Rush Medical College, Chicago, Illinois.

SELECT STUDIES

Mycobacterium avium *Complex*

Moore RD, Chaisson RE. Survival analysis of two controlled trials of rifabutin prophylaxis against *Mycobacterium avium* complex in AIDS. *AIDS*. 1995;9:1337–1342.

This post-hoc analysis of both the original double-blind and open-label follow-up data from two placebo-controlled clinical trials of rifabutin prophylaxis for *Mycobacterium avium* complex (MAC) disease confirmed a trend identified in the original on-treatment analysis suggesting that the use of rifabutin improved survival for patients with AIDS at risk for MAC disease. Data from 1146 patients with HIV and baseline CD4+ cell counts at or below 200/µL were analyzed. Adjusting for Karnofsky score and the occurrence of opportunistic disease, and for use of rifabutin as a time-dependent variable, the relative hazard (RH) of dying while receiving prophylaxis was .74 for the entire cohort ($P < .0004$). For patients with CD4+ cell counts at or below 50/µL, the RH was .75, compared with .69 for those with CD4+ cell counts above 50/µL.

Pierce M, Crampton S, Henry D, Craft C, Notario G. The effect of MAC and its prevention on survival in patients with advanced HIV infection. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

This was the final analysis of a randomized, placebo-controlled clinical trial of clarithromycin for prophylaxis of MAC disease, for which data were initially presented in late 1994. In the study, 642 patients were randomized to received clarithromycin 500 mg bid or placebo. Development of MAC bacteremia in placebo recipients imparted a relative risk of death 2.6 times greater than the risk of death in patients with AIDS without MAC bacteremia. The use of clarithromycin reduced the risk of developing MAC by 69% ($P < .001$) and significantly prolonged the median duration of survival (>700 days compared with 573 days) compared with placebo.

Havlir DV, McCutchan JA, Bozzette SA, Dunne M, and the CCTG/MOPPS Study Investigators. A double-blind randomized study of weekly azithromycin, daily rifabutin, and combination azithromycin and rifabutin for the prevention of *Mycobacterium avium* Complex (MAC) in AIDS patients. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.

This study demonstrated that a weekly dose of azithromycin (1200 mg) may be a more effective alternative to a daily dose of rifabutin (300 mg) as prophylaxis for MAC and that the combination of both drugs is more effective than either single agent. Patients (n = 669) with CD4+ cell counts at or below 100/µL were randomized to receive one of the agents or a combination of the two (same doses). In an intent-to-treat analysis, a significantly lower rate of MAC bacteremia developed in the azithromycin group (13.9%) than in the rifabutin group (23.5%). Fewer events occurred in the combination-treatment group (8.2%) than in the azithromycin ($P = 0.06$) or rifabutin ($P < .001$) groups. There was no difference in survival. No isolates recovered from those randomized to rifabutin alone or azithromycin plus rifabutin were resistant to azithromycin or clarithromycin; however, 11% of those recovered from those receiving azithromycin alone were resistant.

Tuberculosis

Halsey N, Coberly J, Losikoff P, et al. Twice weekly INH vs RIF and PZA for TB prophylaxis in HIV-infected adults. Presented at Second National Conference on Human Retroviruses and Related Infections; January 29–February 2, 1995; Washington, DC.

Preliminary results of this study were presented at the 10th International Conference on AIDS in Yokohama in August 1994. More complete data with additional follow-up were presented here. This is the first study to show that a 6-month (short) course of isoniazid was effective in preventing tuberculosis (TB) among HIV-infected individuals at high risk for TB. Seven hundred and eighty-four PPD-positive Haitian adults with HIV were randomized to receive isoniazid (INH) twice weekly for six months or rifampin and pyrazinamide (RIF/PZA) twice weekly for two months. Ten months after randomization, the Kaplan-Meier estimate of risk of TB was 0.8% and 3.5% for the INH group and the RIF/PZA group respectively ($P = .01$). While longer-term follow-up and additional comparative data are awaited, these results provide some level of comfort that current recommendations for TB prophylaxis for the non–HIV-infected individual may apply to those with HIV infection as well.

Pneumocystis carinii *Pneumonia*

Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1995;332:693–699.

In this open-label study, 843 HIV-infected patients with CD4+ cell counts below 200/µL received zidovudine and either trimethoprim-sulfamethoxazole (TMP-SMX), dapsone, or aerosolized pentamidine. The three agents were shown to be equally effective as initial treatment strategies for the primary prevention of *Pneumocystis carinii* pneumonia (PCP); the estimated 36-month cumulative risk of PCP was 18%, 17%, and 21% in the TMP-SMX, dapsone, and aerosolized pentamidine groups, respectively ($P = 0.22$). This was the first prospective, randomized clinical trial to show that strategies beginning with TMP-SMX or high-dose dapsone were signifi-

cantly more effective than aerosolized pentamidine (estimated cumulative risks 19%, 22%, and 33%, respectively) for patients who initiated PCP prophylaxis at a time when their CD4+ cell counts were below 200/μL.

Simonds RJ, Lindegren ML, Thomas P, et al. Prophylaxis against *Pneumocystis carinii* pneumonia among children with perinatally acquired human immunodeficiency virus infection in the United States. *N Engl J Med.* 1995;332:786–790.

This retrospective study demonstrated that the 1991 guidelines used for initiation of PCP prophylaxis in perinatally HIV-exposed children, which are based on age-specific CD4+ cell count thresholds, failed to identify HIV-exposed infants at risk for PCP sufficiently early to reduce the incidence of disease. A review of 300 medical records of children with PCP revealed that 199 (66%) had never received prophylaxis. Of those, 60 (30%) were first evaluated for HIV at the time of PCP diagnosis and 58 (29%) were first evaluated within 30 days of diagnosis. Of the 28 children who were evaluated more than 30 days prior to diagnosis and for whom CD4+ cell counts were performed during this period, 20 (71%) had no counts below the recommended threshold for prophylaxis. These findings served, in part, as the impetus for revision and publication of new guidelines for offering chemoprophylaxis for PCP to infants perinatally exposed to HIV.

Fungal Infections

Powderly WG, Finkelstein DM, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. *N Engl J Med.* 1995;332:700–705.

This study unequivocally demonstrated that chronic fluconazole prophylaxis was effective in reducing the incidence of cryptococcosis, esophageal candidiasis, and superficial mucocutaneous candidiasis in HIV-infected individuals with CD4+ cell counts below 200/μL. These findings were based on data (median follow-up of 35 months) from 428 patients receiving either fluconazole 200 mg/d or clotrimazole 10 mg five times/d. At entry, the median CD4+ cell count was 90/μL for the fluconazole group and 114/μL for the clotrimazole group. The study also demonstrated greater efficacy of this prophylaxis strategy in those with more advanced immunosuppression (CD4+ cell counts below 50/μL). However, in neither instance was the reduction in the incidence of these fungal complications accompanied by a survival benefit, calling into question the common practice of providing fungal prophylaxis for HIV-infected patients with advanced immunosuppression and no prior systemic fungal disease.

Cytomegalovirus Disease

Spector SA, McKinley G, Drew WL, et al. A randomized, double-blind study of the efficacy and safety of oral ganciclovir for the prevention of cytomegalovirus disease in HIV-infected persons. Presented at Second National Conference on Human Retroviruses and Related Infections; January 29–February 2, 1995; Washington, DC.

This study was the first randomized, placebo-controlled study to demonstrate that daily administration of oral ganciclovir (GCV) reduced the incidence of cytomegalovirus (CMV) end-organ disease in HIV-infected patients with advanced immunosuppression who were CMV positive. Subjects were randomized 2:1 to receive oral GCV 1000 mg q 8h (n = 485) or placebo (n = 289). Median CD4+ cell counts for the two groups were 21/μL and 23/μL, respectively. Treatment was associated with a 50% reduction in the incidence of disease, and oral GCV was generally well-tolerated. This was also the first study to demonstrate that any chemoprophylaxis strategy was capable of reducing the incidence of this disease in patients with AIDS.

Brosgart CL, Craig C, Hillman D, et al. A randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of CMV with severe immunosuppression. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

In contrast to the study reported by Specter et al, this study failed to demonstrate a statistically significant reduction in CMV end-organ disease in patients receiving oral ganciclovir. Subjects received oral GCV (n = 662) or placebo (n = 332); median CD4+ cell count for all patients was 44/μL.

Although the analyses are as yet incomplete, a number of study design differences have been cited as potential explanations for the disparate results, including the fact that baseline ophthalmologic screening exams to exclude asymptomatic CMV retinitis prior to entry were not performed in this study, no routine ophthalmologic or gastrointestinal (GI) evaluations were performed during follow-up unless the patient developed symptoms suggestive of CMV retinitis or GI tract disease. In addition, there was a change midway through the protocol (based on the results of the Syntex-sponsored study reported by Spector et al) allowing patients to crossover to receive oral ganciclovir. The magnitude of the impact of these study design differences on the study results remains to be determined.

Feinberg J, Cooper D, Hurwitz S, et al. Phase III study of valacyclovir (VACV) for cytomegalovirus (CMV) prophylaxis in patients with advanced HIV disease. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

Valacyclovir (VACV) is an oral prodrug of acyclovir that produces plasma levels of acyclovir comparable to those achieved by intravenous acyclovir dosing. This study was the first and only among several conceptually similar studies to show that prophylaxis with VACV reduced the incidence of CMV retinitis in HIV-infected individuals (n = 1227) with advanced immunosuppression (median CD4+ cell count 32/μL). Although the results cannot be statistically compared with those of the oral ganciclovir studies, the magnitude of reduction in the incidence of CMV retinitis was similar to that seen with oral ganciclovir in the placebo-controlled trial reported by Spector et al. There remains a need, however, to identify an appropriately tolerated dose of VACV for this purpose and to clarify the trend suggesting possibly higher mortality in the VACV arm.

COMMENTARY

A number of studies have come to fruition in the past year, the results of which have led to significant advances in our ability to effectively prevent or delay a number of opportunistic infections associated with HIV disease. The studies by Moore et al and Pierce et al showed that chemoprophylaxis with either clarithromycin or rifabutin for disseminated MAC disease results in improved survival for HIV-infected patients with advanced immunosuppression. Disseminated MAC disease and PCP are the only opportunistic infections for which chemoprophylaxis has been associated with a survival benefit. While there remain difficulties in maintaining long-term prophylaxis with rifabutin, clarithromycin, and azithromycin, each has been shown to be effective in reducing the incidence of MAC bacteremia and symptomatic MAC disease. The availability of three active agents offers patients and clinicians options for individualizing prophylaxis strategies. Results of studies directly comparing the macrolides with rifabutin and comparing single-agent prophylaxis with combinations of drugs for prevention of MAC disease are likely to be published in the coming year. While combinations may be more effective than single drugs this comes at an increased cost both in dollars and potentially in toxicity or drug interaction. The outcome of these studies should be examined in detail in the context of what is known about single-agent prophylaxis. The task for the future will be to optimize prophylaxis based on these data and to target those individuals at highest risk with the most effective regimen(s). The latter will require further investigation of diagnostic technologies that will detect and/or predict those at highest risk.

Tuberculosis remains a significant individual and public health hazard for HIV-infected individuals in urban and other high-risk settings. The difficulties many individuals have maintaining adherence to isoniazid prophylaxis over prolonged periods and the uncertainties surrounding appropriate chemoprophylaxis for those exposed to multidrug-resistant strains of *Mycobacterium tuberculosis* highlight the need for more effective prophylaxis. It would appear from the Halsey et al article that a 6-month course of twice weekly isoniazid, one of the recommended regimens for non–HIV-infected persons exposed to or latently infected with drug-susceptible strains of M tuberculosis, may be effective for HIV-infected persons as well. However, shorter-course prophylaxis with multiple drugs may provide a more cost-effective method for reaching the same goal and may expand the spectrum of activity to cover some drug-resistant strains; additional clinical trials further exploring several such regimens are in progress.

Although numerous studies have demonstrated that chemoprophylaxis is effective in significantly reducing the risk of developing PCP, this remains one of the most common HIV-associated opportunistic infections. Trimethoprim-sulfamethoxazole has emerged as the most effective agent, but a substantial portion of HIV-infected individuals remain intolerant to long-term prophylaxis with this drug. Single-agent chemoprophylaxis may fail in a substantial proportion of patients with very advanced immunosuppression. Continued progress in reducing the incidence and risk of this opportunistic complication requires innovative work in developing effective alternatives for those intolerant of or failing currently available regimens, particularly in the setting of profound immunosuppression. No drug can be effective if it is not prescribed by the clinician or used by the patient, and the exploration of factors related to poor adherence, of novel strategies to encourage adherence to therapy, and of strategic education of practitioners and patients alike is necessary.

Systemic and mucosal fungal infections can be effectively prevented with the chronic use of fluconazole. However, this remains an expensive drug, and in the multicenter study evaluating its daily use in a dose of 200 mg, Powderly et al found it was not associated with a survival benefit. A number of case reports and observational studies have suggested that long-term use of fluconazole may lead to development of azole-resistant candidiasis, which, although not usually life-threatening, can be costly and debilitating. Further investigations of more cost-effective chemoprophylaxis regimens that focus on those at highest risk for systemic or invasive fungal disease and of the factors associated with development of azole-resistant candidiasis in those receiving fungal prophylaxis are in progress, as are studies to identify more effective therapies for azole-resistant disease.

Although oral ganciclovir has been approved by the FDA for use in preventing CMV retinitis in HIV-infected patients with advanced immunosuppression, its widespread use for this purpose remains controversial. From one randomized, placebo-controlled trial, Specter et al showed a 50% reduction in the incidence of CMV retinitis. A second similar clinical trial reported by Brosgart et al did not demonstrate a difference between oral ganciclovir and placebo. There were a number of differences between the designs of the two studies that may account for the disparate results. Neither study, however, demonstrated a survival benefit, and there was an insufficient number of end points other than CMV retinitis to draw conclusions regarding the effectiveness of oral ganciclovir for prevention of other CMV end-organ disease. The cost and the number of pills required may pose obstacles to a number of individuals at high risk for CMV disease. Of several studies evaluating high dose oral acyclovir for CMV prophylaxis, only the phase III trial of the prodrug valacyclovir reported by Feinberg has demonstrated a benefit of the agent. Additional studies evaluating quantitative measures of CMV viral load as predictors of development of CMV disease may ultimately point to a manner in which prophylaxis can be earmarked for a patient population likely to derive the most benefit.

The past year has seen significant progress in our ability to delay or prevent opportunistic complications of HIV disease. However, a number of disturbing issues remain. Multiple opportunistic pathogen prophylaxis requires the use of multiple drugs, many of which are associated with significant drug interactions, not only with each other, but also with newly developed classes of antiretroviral agents. The emergence of resistant strains of MAC, M tuberculosis, fungi, and CMV in HIV-infected individuals receiving prophylaxis has posed a challenge to designing effective therapy regimens. These two issues alone underscore the need for continued exploration of the pharmacokinetic and pharmacodynamic interactions between antiretroviral drugs and those used for opportunistic infections and the need for further development of new drugs for opportunistic complications.