

Opportunistic Infection Prophylaxis

Robert L. Murphy, MD, from Northwestern University Medical School in Chicago, reviewed recent information regarding prophylaxis of PCP, toxoplasmosis, and fungal, cytomegalovirus (CMV), and *Mycobacterium avium-complex* (MAC) infections.

Dr Murphy stressed that a number of major issues remain to be confronted in the area of prophylaxis, including whether prevention is associated with survival advantage compared with treatment of acute infection, whether prevented disease is being replaced by infections of other types with no overall survival advantage, and the effect of prophylaxis-induced resistance on delivery of effective therapy for acute infection.

PCP and toxoplasmosis

As related by Dr Murphy, MACS data show that the prevalence of PCP as presenting AIDS diagnosis has declined to the 15% to 20% range since the introduction of prophylaxis; at the same time, there have been increases in the prevalence of MAC infection, wasting syndrome, CMV disease, and esophageal candidiasis. Dr Murphy noted that these data leave unresolved whether the decline in PCP prevalence has been accompanied by prolonged survival. According to these data, approximately 25% of patients ultimately develop PCP despite prophylaxis.

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the agent of choice, although optimal dosage remains a matter of debate, followed by dapsone or aerosolized pentamidine. It is now generally believed that TMP-SMX prophylaxis for PCP also provides protection from toxoplasmosis. The recent published data reviewed by Dr Murphy support superiority of TMP-SMX over other treatment options for PCP prophylaxis and superiority of TMP-SMX and dapsone-pyrimethamine over aerosolized pentamidine in prevention of toxoplasmosis; however, demonstration of survival benefits remains elusive. In a Dutch study, 215 patients received TMP-SMX at either 80/400 mg daily or 160/800 mg daily or 300 mg aerosolized pentamidine monthly as primary prophylaxis. After mean follow-up of 264 days, PCP had developed in none of the TMP-SMX patients and in 11% of pentamidine patients ($P = 0.002$). Although baseline toxoplasmosis serology was not performed, it was observed that three pentamidine patients and no TMP-SMX patients died of toxoplasmosis. In a Spanish study, 166 patients without history of PCP or toxoplasmosis were given double-strength TMP-SMX bid three times weekly or dapsone 100 mg/week plus pyrimethamine 25 mg/week, dosages

characterized as unorthodox by Dr Murphy. During mean follow-up of 380 days, PCP developed in 3.7% of TMP-SMX recipients and 15.2% of dapsone-pyrimethamine recipients ($P = 0.01$). No differences in survival or incidence of toxoplasmosis were observed. TMP-SMX was less well tolerated than dapsone-pyrimethamine. In a French study, 349 patients, 75% of whom were *Toxoplasma* seropositive, received dapsone 50 mg/d or aerosolized pentamidine. PCP rates in the two groups were comparable; however, the relative risk for toxoplasmosis in the pentamidine group was 2.37. In ACTG 021, 310 patients received either TMP-SMX (1 double strength tablet qd) or aerosolized pentamidine as secondary PCP prophylaxis. PCP recurred in 11.4% of TMP-SMX recipients and 27.6% of pentamidine recipients over the course of 18 months, with the CD4+ cell count-adjusted relative risk of PCP in the pentamidine group being 3.25 ($P < 0.001$). No difference in survival rates were observed. Toxicity requiring a switch of therapy occurred in 27% of TMP-SMX and 4% of pentamidine patients. A trend to decreased toxoplasmosis rates was observed in patients who continued to receive TMP-SMX.

Dr Murphy also presented the as-yet unpublished results of ACTG 081, in which 842 patients with CD4+ cell counts $<200/\mu\text{L}$ received one TMP-SMX double-strength tablet bid, dapsone 100 mg/d, or aerosolized pentamidine for primary PCP prophylaxis. As noted by Dr Murphy, the TMP-SMX and dapsone dosages were higher than those commonly used in current practice. Dr Murphy also suggested that the crossover scheme, in which patients exhibiting intolerance were crossed between the TMP-SMX and dapsone arms and thence to the pentamidine arm or randomized from the pentamidine arm to another study arm, may have produced a negative bias for pentamidine and otherwise made some of the findings difficult to interpret. Analysis of outcome by original treatment showed no major differences among the TMP-SMX, dapsone, and pentamidine groups with regard to PCP rates (9.8%, 8.6%, and 14.0%, respectively, at 24 months, and 17.6%, 16.5%, and 20.7%, respectively, at 36 months), all-cause mortality rates (19.7%, 23.2%, and 23.2%, respectively at 24 months, and 42.7%, 48.2%, and 48.2%, respectively, at 36

months), or toxoplasmosis rates, although analysis among patients beginning with CD4+ cell counts $<100/\mu\text{L}$ showed a significant PCP-preventive effect for the systemic treatments ($P = 0.03$). Switching of treatment occurred significantly less frequently among patients beginning treatment with pentamidine ($P < 0.0001$), with crossover due to intolerance occurring in 50.7%, 41.3%, and 12.0% of TMP-SMX, dapsone, and pentamidine recipients, respectively. Dr Murphy emphasized that only 7% of the failures overall were actually receiving TMP-SMX at the time of development of PCP. Fever, rash, and granulocytopenia were more common among patients receiving the systemic treatments; however, despite the frequency of intolerance of TMP-SMX, use of aerosolized pentamidine was not asso-

- **Recent PCP prophylaxis studies tend to support superiority of TMP-SMX: parenteral pentamidine successful in patients not tolerating other treatments**
- **Fluconazole associated with significant prevention of fungal infection, including invasive disease and cryptococcosis, but no mortality benefit in ACTG 981**
- **Uveitis associated with rifabutin MAC prophylaxis**

ciated with advantages in terms of disability, utilization of health care services, or health-related quality of life. According to Dr Murphy, one of the conclusions to be drawn from the study is that higher doses of TMP-SMX and dapsone are not well tolerated; he also maintained that such dosages may not be necessary.

With regard to other treatment options, Dr Murphy related that a retrospective review of the use of parenteral, primarily intramuscular, pentamidine in 96 patients intolerant of TMP-SMX, dapsone, and aerosolized pentamidine showed that only three cases of PCP occurred during 350 months of primary prophylaxis in 47 patients and 426 months of secondary prophylaxis in 49 patients; eight significant but non-life-threatening adverse reactions (sterile abscesses, glucose intolerance, hypotension, and hypoglycemia) were reported. According to Dr Murphy, findings showing lack of tolerance of clindamycin in clindamycin-pyrimethamine regimens indicate unsuitability of the regimen for prophylaxis. Azithromycin also is not

considered a likely candidate for use. Atovaquone, which recently has been approved for treatment of mild to moderate PCP, is to be compared with dapsone in a large-scale prophylaxis study in TMP-SMX-intolerant patients; Dr Murphy cautioned that since atovaquone is poorly absorbed in its current formulation, requiring administration along with a high-fat snack, prophylactic use is difficult and probably requires full treatment doses.

Fungal infection

Cryptococcosis develops in 5% to 10% of AIDS patients not receiving prophylaxis and generally occurs at CD4+ cell counts <100/ μ L. In ACTG 981, involving 428 of the patients enrolled in ACTG 081 PCP study, patients were randomized to fluconazole 200 mg/d or clotrimazole troches 10 mg five times daily for prevention of fungal infection. Fluconazole was associated with significant reductions in the incidence of invasive fungal disease (9 vs 23 patients) and cryptococcosis (2 vs 15 patients); the 24-month risk of invasive disease was 2.8% in the fluconazole group and 9.1% in the clotrimazole group, and the CD4+ cell count-adjusted relative risk for invasive disease in the latter group was 3.25. Fluconazole was also associated with significant reductions in the incidence of esophageal candidiasis (3 vs 20 patients) and superficial fungal infection (10 vs 36 patients). No differences in mortality were observed, however. Dr Murphy maintained that such findings leave it unclear whether fluconazole prophylaxis should be utilized, given the absence of survival benefit, the low lethality of properly managed first-episode cryptococcosis, and the potential for development of resistance to an otherwise highly useful agent; he stated, however, that if prophylaxis is contemplated, fluconazole appears to be the azole of choice, since it does not have the absorption problems associated with ketoconazole or itraconazole, and suggested that fluconazole prophylaxis would be optimally begun at CD4+ cell counts below 100/ μ L and at a dosage lower than that investigated in the study (eg, on the order of 100 mg/d).

CMV infection

Recent data indicate that approximately 40% of patients with CD4+ cell counts below 50/ μ L develop CMV retinitis within a 27-month period. Currently, no agents suitable for prophylactic use are available. Trials of an oral form of ganciclovir are under way, and study of oral forms of foscarnet has been initiated in the United Kingdom. One European-Aus-

tralian study evaluating high-dose acyclovir (3200 to 4000 mg/d) found no protective effect against CMV disease, but documented an increase in survival in acyclovir-treated patients; according to Dr Murphy, recent MACS data may provide some support of an acyclovir-associated survival benefit.

MAC infection

MAC infection has been observed to occur in more than half of patients within 24 to 30 months following diagnosis of AIDS. On the basis of two studies involving approximately 1000 patients showing that rifabutin provided significant protection from development of MAC bacteremia, it was recommended in June 1993 that prophylaxis at a dosage of 300 mg/d be considered for patients with CD4+ cell counts below 100/ μ L. Azithromycin and clarithromycin have activity against MAC and a large-scale trial comparing rifabutin plus clarithromycin and clarithromycin in MAC prophylaxis currently is under way. In noting that many practitioners are al-

ready using clarithromycin for prophylaxis, Dr Murphy suggested a more prudent current course might be to reserve the agent for treatment.

As noted by Dr Murphy, daily doses of rifabutin should not exceed 300 mg given recent reports of uveitis in higher-dose trials. Although uveitis was not observed at dosages of at or below 600 mg/d in initial studies, 23 cases have been reported in a Canadian treatment study in which patients are receiving rifabutin 600 mg/d, clarithromycin 1000 mg bid, and ethambutol 15 mg/kg/d; uveitis also has been observed in 11 of 1215 patients enrolled in an ongoing US ACTG/Community Programs for Clinical Research on AIDS trial. The uveitis has been reported to resolve with drug withdrawal or dose reduction. It is believed that there may be a bidirectional drug interaction between clarithromycin and rifabutin that increases blood levels of both agents. Further, it is known that fluconazole may increase rifabutin levels by as much as 80%, warranting caution in the concomitant use of these agents. ■

Future Directions for Anti-HIV Therapy

Future directions for anti-HIV therapy were discussed at the Chicago meeting by Douglas D. Richman, MD, from the University of California San Diego and the San Diego Veterans Affairs Medical Center, and at the Los Angeles meeting by Steven A. Miles, MD, from the University of California Los Angeles.

According to Dr Richman, the conclusion beckoning from the current status of antiretroviral therapy is that combination therapy will be required to improve effectiveness of treatment and that agents in addition to the nucleoside analogues are needed. Dr Richman identified the NNRTIs and protease inhibitors as classes of newer agents that show promise of utility.

NNRTIs: nevirapine

As stated by Dr Richman, data on the several NNRTIs under development indicate that the compounds have potent anti-HIV activity but rapidly select for drug resistance. Data from a group of patients receiving nevirapine at Dr Richman's institution show that resistance appears rapidly in virtually all patients, regardless of whether the drug is administered alone or in combination with zidovudine, and is evident as early as 1 week after the start of treatment. Several specific RT mutations associated with resistance have been identified, with those observed under monotherapy generally differing in distribution from those observed under combination therapy with zidovudine. Typical responses to low-dose

nevirapine monotherapy have consisted of an impressive increase in CD4+ cell count within a week of treatment but a return to baseline levels within 1 month due to acquisition of drug resistance. However, the use of higher doses in an attempt to achieve plasma levels sufficient to exceed viral resistance – an attempt encouraged by the absence of dose-limiting toxicity at lower doses – has shown that many patients have markedly prolonged response to high-dose monotherapy. The median CD4+ cell count in patients with higher baseline CD4+ cell counts receiving a dosage of 400 mg/d increased about 75 cells/ μ L for 9 to 12 months. A similar maintenance of decreases in p24 antigen levels and PCR quantitated HIV RNA levels has been observed in patients.

Dr Richman emphasized that such a response is not seen in all patients receiving a higher dosage and that factors predictive of such response remain undetermined. Nevertheless, he stated that these findings and data from another group utilizing monotherapy and combination therapy in newborns indicate that the agent may have a role in some patients. The rationale for use despite the observation of resistance is that