Treatment of Opportunistic Infections

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Dr Powderly was invited by the IAS-USA to select the key clinical findings presented or published in the last year on the treatment of opportunistic infections and to provide a commentary on the current status of this treatment area. Dr Powderly is Associate Professor of Medicine at the Washington University School of Medicine in St. Louis, Missouri.

SELECT STUDIES

Oral Ganciclovir European and Australian Cooperative Study Group. Intravenous versus oral ganciclovir: European/Australian comparative study of efficacy and safety in the prevention of cytomegalovirus retinitis recurrence in patients with AIDS. *AIDS*. 1995;9:471–478.

Drew WL, Ives D, Lalezari JP, et al. Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. *N Engl J Med*. 1995;333:615–620.

These two articles support the use of oral ganciclovir as maintenance therapy after intravenous (IV) ganciclovir induction in select patients with non–sight-threatening cytomegalovirus (CMV) retinitis. In the European/Australian study, 159 patients with AIDS and stable CMV retinitis following an induction course with IV ganciclovir were randomized to receive maintenance therapy with oral ganciclovir (500 mg six times/d) or IV ganciclovir (5 mg/kg once daily infused over 1h). By masked assessment of fundus photographs, investigators found a mean time to progression of 51 days with oral ganciclovir and 62 days with IV ganciclovir ($P = .15$). As determined by funduscopy, mean time to progression was 86 days and 109 days, respectively ($P = .02$).

Similarly, Drew et al found that mean times to progression among 115 patients on the basis of masked assessment of retinal photographs were 62 days in the IV group and 57 days in the oral group ($P = .63$), compared with 96 days and 68 days, respectively ($P = .03$), on the basis of funduscopy by ophthalmologists who knew treatment assignments. In both studies there was no significant difference between the two groups in terms of adverse events. Neutropenia, anemia, sepsis, and other catheter-related adverse events were more common in the IV group, and diarrhea was more common in the oral groups. In addition, Drew et al found no significant difference between groups in the incidence of viral shedding or survival.

The Chiron Ganciclovir Implant Study Group. A randomized controlled multicenter clinical trial of a sustained-release intraocular ganciclovir implant in AIDS patients with CMV retinitis. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

Intraocular ganciclovir is an extremely effective way of achieving local control of retinitis; however, it needs to be combined with systemic therapy because of the high risk of subsequent disease in the other eye or elsewhere. In this study, patients with newly diagnosed CMV retinitis received ganciclovir either IV or as an implant of 1 µg/h or 2 µg/h. Overall, median times to progression were 216 days in the combined implant groups and 104 days in the IV group ($P < .0001$). No significant differences in survival or fellow-eye involvement were observed. However, 15.3% of the implant group developed extraocular CMV disease and complications in the group included retinal detachment in 5.2% and endophthalmitis in 1.2%.

Lalezari J, Holland G, Stagg R, et al. A randomized, controlled study of cidofovir (CDV) for relapsing cytomegalovirus retinitis (CMV-R) in patients with AIDS. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

Results from this preliminary analysis demonstrate that cidofovir is clearly effective; however, nephrotoxicity may limit its usefulness. Patients with CMV-R progression despite systemic ganciclovir and/or foscarnet, and/or intolerance to either agent were randomized to receive an induction course of CDV 5mg/kg once weekly for 2 weeks (induction) and then 5 mg/kg once every other week (Group A), or 3 mg/kg once every other week (Group B). IV normal saline and oral probenecid were given to minimize potential nephrotoxicity. This interim intent-to-treat analysis of the first 60 patients found a median time to CMV-R of 115 days (Group A) compared with 49 days (Group B) (log-rank test $P = .12$). Seven percent of patients in both groups developed a serum creatinine greater than or equal to 2 mg/dL. Mild-to-moderate probenecid reactions occurred in 48% of patients.

Shafran SD, Singer J, Phillips P, and the Canadian MAC Study Group. The Canadian randomized open-label trial of combination therapy for MAC bacteremia: final results. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

In this open-label trial, 229 HIV-infected adults with MAC bacteremia were randomized to receive four drugs (ciprofloxacin 750 mg bid, ethambutol 15 mg/kg qd, rifampin 600 mg qd, and clofazimine 100 mg qd) or three drugs (clarithromycin 1000 mg bid, rifabutin 600 mg qd, and ethambutol 15 mg/kg qd). The rifabutin dose was halved to 300 mg qd following the development of uveitis in a sizable number of patients. In analysis done on 187 patients, MAC bacteremia was cleared in 67/97 (89%) of patients in the three-drug arm compared with 26/90 (29%) of patients on the four-drug arm (log-rank test, $P < .001$). Clearance was higher for the three-drug arm at both doses of rifabutin. Median survival times were 8.7 and 5.2 months for patients in the three- and four- drug arms, respectively (log-rank test, $P < .001$). Clarithromycin-based therapeutic regimens are more effective in clearing *Mycobacterium avium* complex (MAC) bacteremia and pro-

long survival. These results should end debate about whether MAC is a disease that should be treated.

May T, Brel F, Beuscart C, et al. A French randomized open trial of 2 clarithromycin combination therapies for MAC bacteremia: first results. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

Dube MP, Sattler F, Torriani F, et al. A randomized study of clarithromycin plus clofazimine, with or without ethambutol, for treatment and prevention of relapse of disseminated MAC in AIDS. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.

These two studies suggest that giving clofazimine alone as adjunctive therapy to clarithromycin may not delay the emergence of clarithromycin resistance. In the French open-label trial, HIV-infected adults with MAC bacteremia and no prior treatment with clarithromycin were randomized to Group A (clarithromycin 2000 mg bid 2 months then 1000 mg bid and clofazimine 200 mg qd 2 months then 100 mg qd) or Group B (clarithromycin (same dose), rifabutin 450 mg qd and ethambutol 1200 mg qd). One-hundred and twenty-three patients were evaluated during interim analysis. Mean CD4+ cell count was 14/μL; median Karnofsky index was 70. Success was defined as the patient being alive, with a decrease of fever and negative blood culture. At 2 months and 6 months, there was no difference between groups on these criteria or in survival distribution. Fourteen patients in Group A and two patients in Group B acquired resistance to clarithromycin ($P < .01$).

In the study reported by Dube and colleagues for the California Collaborative Treatment Group, patients with AIDS and disseminated MAC were randomized to receive clarithromycin 2 g/d and clofazimine 100 mg/d, with or without ethambutol 80 mg/d. Sixty-nine percent of patients in both the 2-drug and 3-drug arms responded to therapy. Based on a blinded, post-hoc analysis, defining relapse as any positive culture following response, investigators determined risk estimates for relapse at 36 weeks to be 91% for the 2-drug arm and 50% for the 3-drug arm ($P = .014$). Twenty-one of 27 relapse isolates were clarithromycin-resistant; median time to development of resistance was 16 weeks with two drugs and 40 weeks with three drugs ($P = .004$).

Van der Horst C, Saag MS, Cloud G, et al, the NIAID AIDS Clinical Trials Group and Mycoses Study Group. Part 1. Randomized double blind comparison of amphotericin B (AMB) plus flucytosine to AMB alone (step 1) followed by a comparison of fluconazole to itraconazole (step 2) in the treatment of acute cryptococcal meningitis in patients with AIDS. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

Saag M, Van der Horst C, Cloud G, et al, the NIAID AIDS Clinical Trials Group and Mycoses Study Group. Part 2. Randomized double blind comparison of amphotericin B (AMB) plus flucytosine to AMB alone (step 1) followed by a comparison of fluconazole to itraconazole (step 2) in the treatment of acute cryptococcal meningitis in patients with AIDS. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

The optimal therapy for acute cryptococcal meningitis seems to be an initial period of amphotericin B plus flucytosine (FC) followed by fluconazole (FLU). In this two-part study, 408 patients with a first episode of cryptococcal meningitis and <1 mg/kg prior AMB were randomized to receive AMB .7 mg/kg/d for 14 days or AMB (same dose) plus FC 100 mg/kg/d for 14 days. The median CD4+ cell count was 18/μL. Analyses at 14 days determined that survival was similar in both groups; CSF sterilization was increased in the combination group ($P = .06$); and there was no difference between groups in terms of toxicity.

The objective of Step 2 was to demonstrate that the efficacy of ITRA was close to that of FLU. Patients who had received a minimum total dose of AMB 7.5 mg/kg in Part 1, had improved or stable mental status, were able to take oral drugs, and were not receiving antiseizure medication or rifamycins, were randomized to receive FLU 400 mg qd, or itraconazole (ITRA) 200 mg bid for 8 weeks. Investigators determined that the CSF sterilization was 72% and 60% for the FLU and ITRA groups, respectively, and that clinical response was 68% and 70% respectively. The overall mortality for the trial was 6%.

Saag MS, Cloud GC, Graybill JR, et al, the NIAID ACTG and Mycoses Study Group. Comparison of fluconazole versus itraconazole as maintenance therapy of AIDS-associated cryptococcal meningitis. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

Fluconazole is clearly the maintenance therapy of choice for cryptococcal disease. In this phase III double-blind comparison, patients who had been successfuly treated for cryptococcal meningitis within the last 4 months (negative CSF fungal culture and no clinical symptoms) were randomized to receive FLU 200 mg/d or ITRA 200 mg/d. Among 107 patients observed for 52 weeks, 2/52 (3.8%) assigned to FLU and 13/55 (23.6%) patients assigned to ITRA had documented CSF culture-positive relapses ($P = .003$). None of the 19 deaths during the study was due to cryptococcal disease; both drugs were well tolerated.

COMMENTARY

Cytomegalovirus Infections

Although there were no dramatic breakthroughs in terms of new agents for the treatment of CMV infections, two developments in the delivery of ganciclovir have potential for a major therapeutic impact. Data from two large randomized comparative trials—reported by the Oral Ganciclovir European and Australian Cooperative Study Group and by Drew et al—seemed to confirm that the oral formulation of ganciclovir in a dose of 3000 mg qd is as effective as IV ganciclovir in delaying progression of CMV retinitis after initial induction therapy with the IV drug. There remains some doubt, however, regarding exactly what the trials show, since the results are open to several interpretations. In both trials, when the two treatment strategies were compared using retinal photographs, the mean time to progression of retinitis was similar. However, the oral drug appeared less successful in delaying progression when the assessment of progression was based on direct examination by ophthalmologists. The latter finding may reflect bias, since the ophthalmologists in both trials knew which treatment the patient was receiving, or it may reflect true subtle progression picked up by experienced clinicians. Oral ganciclovir is poorly absorbed, having a bioavailability of less than 10%, so it is not unreasonable to expect it to be somewhat less effective. The observation of reduced efficacy is supported by the fact that for patients entering the studies with unilateral retinitis, retinitis was more likely to develop in the uninvolved eye in patients receiving oral ganciclovir. However, patients on oral drug do not need long-term in-dwelling catheters and have a better quality of life. Consequently, although probably not best suited for patients with sight-threatening retinitis, oral ganciclovir is a useful alternative for select patients.

In contrast, ganciclovir intraocular implants represent a clearly more effective way of delaying the progression of retinitis. The Chiron Ganciclovir Implant Study Group and others[1] reported that the implants were associated with a median time to progression that is superior to that associated with IV ganciclovir. However, it is clearly local therapy, because almost half of all patients treated just with implants developed either retinitis in the other eye or systemic CMV infection. In addition, early surgical complications, such as endophthalmitis and retinal detachment, occurred in 10% to 20% of patients. Although the role of such local therapy needs to be further defined, a combination of local and systemic therapy may lead to more effective control of disease and warrants further study.

This past year Lalezari et al and others[2] reported early promising data on the use of cidofovir given both IV and intraocularly in CMV retinitis. Although parenteral use of the agent may be limited by nephrotoxicity, the results of ongoing trials should allow for a better assessment of the role of this agent.

Disseminated Mycobacterium avium *Complex Infection*

It has become increasingly apparent that MAC infection is associated with reduced survival and that therapy for MAC improves survival. The availability of the macrolides in MAC treatment has also been shown to correlate with an improved outcome for patients with MAC. The AIDS Clinical Trials Group (ACTG) study of clarithromycin monotherapy published in late 1994 demonstrated both considerable efficacy and some limitations of this drug.[3] All three dosage regimens studied (1 g, 2 g, or 4 g per day) effectively cleared bacteremia and decreased symptoms. A dose-response relationship was observed. The highest dose produced the most rapid response, but also was associated with the greatest amount of gastrointestinal toxicity. Relapses, associated with microbiologic resistance, were common and an unexpectedly higher (and unexplained) risk of death was noted in patients receiving higher doses.

Clarithromycin-based regimens have become the standard of care. Initial results of several trials suggest that this is appropriate. In the Canadian study reported by Shafran et al, comparison of a three-drug macrolide-based regimen (clarithromycin, ethambutol, and rifabutin) with a four-drug regimen (clofazimine, ciprofloxacin, ethambutol, and rifampin) previously evaluated by the Canadian Clinical Trials Group (CCTG) demonstrated not only a significantly better rate of clearance of MAC bacteremia (69% vs 30%) but also a significantly longer survival (8.7 months vs 5.2 months) in patients receiving the three-drug clarithromycin-containing regimen.

The issue of which drugs are best used with clarithromycin is still being evaluated, but initial data from two trials suggest that clofazimine is not optimal. The French study reported by May et al, which compared clarithromycin plus clofazimine with clarithromycin plus ethambutol and rifabutin, indicated that clarithromycin resistance was more likely in patients who received clofazimine. In the trial of clarithromycin and clofazimine with or without ethambutol reported by Dube et al, the rate of development of resistance was also higher in patients who received just clofazimine and clarithromycin. This year should bring the results of several additional large trials that may clarify the best available therapy for disseminated MAC.

Cryptococcal Meningitis

In fungal disease management, the most significant event was the presentation of the results of two large trials by the National Institute for Allergy and Infectious Diseases (NIAID) ACTG and the Mycoses Study Group that evaluated the initial and maintenance treatment of cryptococcal meningitis. Previous studies had suggested that patients treated with amphotericin B tended to have more rapid cerebrospinal fluid (CSF) clearance than did patients treated with azoles. Since the major limitations of amphotericin B are toxicity and the need for parenteral administration, these observations led the Mycoses Study Group and ACTG investigators to perform a trial of initial amphotericin B therapy (with or without concomitant flucytosine) followed by a "consolidation" period of triazole therapy with high doses of either fluconazole or itraconazole. The results of this trial suggest that this approach is very successful, at least compared with previous experience, in the majority of patients. The acute mortality (first 2 weeks) in this trial was 6% and the overall mortality 8%. There was a trend that approached significance for a better microbiologic outcome (clearance of organisms from CSF) at 2 weeks for patients assigned to receive flucytosine and at 10 weeks for patients assigned to fluconazole. The high-dose amphotericin B regimen was well tolerated, and flucytosine appeared to add little additional toxicity. Further support for this approach to disease management comes from data from an Italian center[4] where all patients were treated for 14 days with high-dose (1 mg/kg/d) amphotericin B, followed by maintenance fluconazole or itraconazole. Of 31 patients treated in this fashion, 29 (94%) responded to therapy and there were no deaths due to cryptococcosis. When the Mycoses Study

Group compared fluconazole and itraconazole as maintenance therapy, results clearly demonstrated that fluconazole was superior. It is of interest that a multivariate analysis of predictors of relapse showed that receiving flucytosine as part of the initial induction therapy was associated with a lower risk of recurrence. One interpretation of these results might be that the better initial microbiologic control of infection seen with amphotericin B and flucytosine in combination might be reflective of better overall response and possibly even cure.

REFERENCES

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