

OPPORTUNISTIC INFECTIONS IN THE ERA OF POTENT ANTIRETROVIRAL THERAPY

Issues regarding the incidence and presentation of opportunistic infections (OIs) in patients taking potent antiretroviral regimens and the prospects for discontinuing OI prophylaxis or maintenance treatment after CD4+ cell count increases under such therapy were discussed by Judith A. Aberg, MD, at the San Francisco course.

The incidence of opportunistic infections (OIs) has decreased dramatically since the introduction of potent antiretroviral therapy. Decreases in incidence, however, were observed prior to the use of these potent regimens, likely in association with earlier intervention with OI prophylaxis and use of dual nucleoside reverse transcriptase inhibitor (nRTI) treatment. Recently, a modest increase in incidence of several OIs has occurred at San Francisco General Hospital. Although some of these incidences reflect infections in previously untreated patients, others are associated with virologic failure of treatment or consist of unusual manifestations of infections following initiation of potent antiretroviral therapy. These unusual manifestations have been observed by other investigators as well.

PARADOXICAL WORSENING OF OIS UNDER ANTIRETROVIRAL THERAPY

In a report by Narita and colleagues, paradoxical worsening of tuberculosis was observed in 12 of 33 HIV-1-infected patients treated simultaneously with an antituberculosis regimen and antiretroviral therapy, characterized by increased lymphadenopathy, fevers, and pleural effusion. By comparison, paradoxical worsening was observed in only 1 of 55 HIV-seronegative patients and in 2 of 28 HIV-infected patients receiving antituberculosis treatment but not antiretroviral therapy. The paradoxical responses were

observed sooner in patients receiving simultaneous treatment (15 days) than in those who did not (109 days). Among the patients receiving simultaneous treatment, no differences in CD4+ cell count were observed between those who exhibited paradoxical worsening and those who did not. Tuberculin antigen testing in 8 of the patients receiving simultaneous treatment showed a positive test in 1 patient prior to initiation of treatment and the development of a positive response in 6 of the remaining 7 patients during follow-

Unusual presentations and paradoxical worsening of OIs have been observed in patients starting potent antiretroviral therapy

up, suggesting that some immune reconstitution had occurred during antiretroviral therapy.

Phillips and colleagues reported 9 cases of *Mycobacterium avium* complex (MAC) lymphadenitis in patients within 12 weeks of beginning potent antiretroviral therapy. These patients had a mean nadir CD4+ cell count of 37/ μ L and a mean count at presentation of 150/ μ L. Only 1 patient developed mycobac-

teremia. It is probable that these cases reflect the consequence of a restored pathogen-specific immune response to subclinical localized infection at the time of initiation of antiretroviral therapy. In other cases reported by Woods and colleagues, subclinical cryptococcal infection has appeared to rapidly present as meningitis soon after initiation of antiretroviral therapy. In 1 patient, meningitis occurred after 4 days of triple therapy and an increase in CD4+ cell count from 5 to 70/ μ L. In another, meningitis occurred 15 days after the addition of saquinavir and stavudine to existing lamivudine treatment and an increase in CD4+ cell count from 30 to 110/ μ L. In a third patient with a history of cryptococcal meningitis who had received acute treatment and was receiving itraconazole, culture-negative meningitis occurred 10 days after initiation of triple antiretroviral therapy and an increase in CD4+ cell count from 40 to 240/ μ L.

DYNAMICS OF CELLULAR RESTORATION AFTER ANTIRETROVIRAL THERAPY

A number of studies have reported that the initial rise in CD4+ cell count is comprised primarily of memory CD4+ T cells, with a more gradual rise in naive CD4+ T cells occurring after 12 to 24 weeks and continuing for years. Autran and colleagues observed reduction in CD8+ activation indicated by eventual decline in memory CD8+ T cells, as well as an increased lymphoproliferative response to CMV and tuberculin recall antigens. In ACTG 315 similar dynamics were observed. Treatment with zidovudine followed at day 10 by zidovudine/lamivudine in patients with CD4+ cell counts of 100 to 300/ μ L resulted in an initial increase in all lymphocytes except natural killer cells, followed by a gradual increase in naive CD4+ and CD8+ T cells. Levels of memory CD8+ T cells declined after an initial

TABLE 1. SELECTED CLINICAL TRIALS EVALUATING THE DISCONTINUATION OF PROPHYLAXIS OR MAINTENANCE THERAPY

Trial	Target Accrual (No. Patients)	Schema
ACTG 360*	300	Prospective observational study of development of CMV in patients who have had CD4+ <50/ μ L within past 24 months and no history of active CMV disease
ACTG 362*	636	MAC prophylaxis study: azithromycin versus placebo in patients whose CD4+ counts were once <50/ μ L and are now >100/ μ L on potent antiretroviral therapy
CPCRA 048	850	Similar to ACTG 362, but also evaluating risk of bacterial pneumonia
ACTG 379	125	Discontinuation of CMV maintenance therapy
ACTG 393	50	Discontinuation of MAC maintenance therapy
ACTG 888*	250	Discontinuation of primary and secondary prophylaxis
ACTG 5038*	50	Discontinuation of histoplasmosis therapy
CFAR	10	Discontinuation of cryptococcal maintenance therapy

ACTG indicates AIDS Clinical Trials Group. CPCRA indicates Community Programs for Clinical Research of AIDS. CFAR indicates Center for AIDS Research Pilot Study.

*ACTG 360 and 362 and ACTG 888 primary prophylaxis arm have been fully accrued and are closed to enrollment. ACTG 5038 opened in April 1999.

Adapted from Aberg JA. *Formulary*. 1999;34:418–434.

increase, likely reflecting decreased activation in the context of reduced viral antigen.

Return of cell-mediated immune response has been observed by several investigators. Komanduri and colleagues compared CMV antigen-specific CD4+ T-cell responses measured by flow cytometry in 4 groups: HIV-infected patients with active CMV retinitis, those with quiescent CMV retinitis in whom increased CD4+ cell counts had permitted withdrawal of maintenance therapy, those who were CMV antibody-positive without disease, and subjects who were HIV-seronegative and CMV-seropositive. Patients with quiescent CMV disease had responses similar in magnitude to HIV-infected patients who were CMV-seropositive only and to HIV-seronegative/CMV-seropositive subjects. Patients with

active CMV disease had reduced responses. Torriani and colleagues also found increased CMV-specific CD4+ cell proliferative response on lymphoproliferative assays in 8 of the 11 patients in whom CMV maintenance therapy was withdrawn after increases in CD4+ cell count. Of the 3 patients without an initially observed response, 1 developed retinitis, 1 developed a CMV-specific CD4+ cell response 6 months later, and 1 has exhibited neither response nor relapse of CMV disease. In the additional relapses in this group, the decline in CD4+ cell count to below 50/ μ L was associated with loss of the CMV-specific CD4+ cell response. In addition to indicating that the CD4+ cell count increase under potent antiretroviral therapy is associated with restoration of antigen-specific responsiveness, these studies suggest that use of

assays to determine when such a response is present may provide a means of determining when prophylaxis or maintenance therapy for OIs can safely be withdrawn. However, other studies using such assays to determine in vitro antigen-specific responses have yielded disparate results, indicating absence of clear correlation of assay findings with clinical status. Thus, until immunoassays are standardized and validated, it remains unclear if they can be used to predict which patients might be at risk of disease development or recurrence.

Despite evidence that CD4+ cell count increases are protective and associated with reconstitution of antigen-specific responses, basic questions remain about the nature of immune reconstitution associated with potent antiretroviral therapy, including the degree to which naive cell increases may contribute to restoration of “lost” immune response; whether immunization can be active in restoration of lost response; the degree to which immune restoration continues with continued suppression of viral load; and the immunologic consequences of viral rebound during antiretroviral therapy.

PROPHYLAXIS/MAINTENANCE THERAPY AFTER INITIATION OF ANTIRETROVIRAL THERAPY

The observation of immune reconstitution following initiation of potent antiretrovi-

Data indicate that prophylaxis or maintenance treatment for some OIs can be safely withdrawn with sustained increases in CD4+ cell count

1999 USPHS/IDSA GUIDELINES FOR THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN PERSONS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

In 1995, the USPHS and the IDSA developed guidelines for preventing OIs in persons infected with HIV. These guidelines, written for health care providers and patients, were revised in 1997. Because important new data concerning the prevention of opportunistic diseases have emerged since 1997, the USPHS and the IDSA reconvened the Prevention of Opportunistic Infections Working Group on March 4 and 5, 1999, to determine which recommendations warranted revision. Much attention was focused on recent data related to the advisability of discontinuing OI prophylaxis (primary prophylaxis and prophylaxis against recurrence) among persons whose CD4+ cell counts have increased to above prophylaxis thresholds because of potent antiretroviral therapy. The OI Working Group also addressed 2 pathogens not previously considered—human herpesvirus type 8 and hepatitis C virus. In addition, working group members reviewed data concerning the prevention of all common HIV-associated OIs.

PRIMARY CHANGES IN RECOMMENDATIONS

Primary changes in the disease-specific recommendations include:

- The addition of statements concerning discontinuation of prophylaxis against specific OIs when the CD4+ cell count increases in response to potent

antiretroviral therapy

- New recommendations regarding human herpesvirus type 8 and hepatitis C virus.
- New recommendations concerning injection drug users.
- New recommendations about short-course chemoprophylaxis against tuberculosis in HIV-infected persons with positive tuberculin skin tests.
- Changes in secondary prophylaxis (chronic maintenance therapy) recommended to prevent the recurrence of *Mycobacterium avium* complex and cytomegalovirus disease.
- Caution against using fluconazole during pregnancy.
- Statements concerning the use of varicella and rotavirus vaccines among HIV-infected infants.

These guidelines were made available for public comment through announcements in the *Federal Register* and the *MMWR*. The final document is endorsed by the USPHS and IDSA as well as by the Infectious Diseases Society of Obstetrics and Gynecology and the National Foundation for Infectious Diseases.

A complete copy of the new recommendations can be found on the CDC Web page at http://www2.cdc.gov/mmwr/mmwr_rr.html.

This announcement is adapted from MMWR Morb Mortal Wkly Rep. 1999;48(RR10):1-59.

ral therapy has raised issues regarding if and when prophylaxis or maintenance therapy for OIs can be discontinued. Reports indicate that with increases in CD4+ cell count, discontinuation of prophylaxis or maintenance treatment is associated with relapse of disease only infrequently.

Dr Aberg and colleagues discontinued antimycobacterial therapy in 4 patients following 12 months of treatment

for disseminated MAC disease after initiation of antiretroviral therapy resulted in increases in CD4+ cell counts to above 100/ μ L. Sterile bone aspirate and peripheral blood cultures for MAC were obtained prior to discontinuation of anti-MAC therapy. CD4+ cell counts were 4 to 5/ μ L at the time of diagnosis of disseminated MAC disease in these patients and 137 to 301/ μ L at the time of discon-

tinuation of MAC therapy; plasma HIV RNA levels were below 500 copies/mL in 3 patients and 1250 copies/mL in 1 patient when MAC therapy was discontinued. No relapses have been observed in these patients during 17 to 22 months of follow-up. Dr Aberg and colleagues are participating in the ongoing ACTG 393 study of withdrawing MAC therapy; in early follow-up, no relapses have been observed in the first 16 patients enrolled.

In a report by Tural and colleagues, 7 patients who discontinued maintenance therapy for cytomegalovirus (CMV) retinitis after 3 months of potent antiretroviral therapy had increased CD4+ cell counts to greater than 150/ μ L and maintained plasma HIV RNA levels at less than 200 copies/mL. No relapses were observed in these patients during 9 to 12 months of follow-up; subsequently, 1 patient has relapsed in association with a decrease in CD4+ cell count to below 50/ μ L. Investigators at the University of California San Diego reported that 11 patients who discontinued CMV maintenance therapy after antiretroviral therapy had increased CD4+ cell counts from a median of 42/ μ L to a median of 183/ μ L; only 3 of the 11 patients had plasma HIV RNA levels below the limit of assay detection. No relapses were observed in these patients over a period of 6 to 18 months of follow-up, despite absence of maximal suppression of viral load. Subsequently, relapse has occurred in 3 patients in association with CD4+ cell count declines to below 50/ μ L.

A number of reports indicate the absence of occurrence of *Pneumocystis carinii* pneumonia (PCP) following withdrawal of primary or secondary prophylaxis in patients with CD4+ cell count increases above 200/ μ L on potent antiretroviral therapy. For example, investigators from the Netherlands reported no occurrences of PCP over 7 to 14 months following withdrawal of primary prophylaxis in 62 patients and secondary prophylaxis in 16 patients with CD4+ cell count increases above 200/ μ L; at the time of discontinuation, the mean CD4+ cell count was 346/ μ L and plasma viral load was below assay detection limit in 61 patients. Two patients reinitiated prophylaxis when their CD4+ cell count dropped below 200/ μ L.

RECOMMENDATIONS ON DISCONTINUING PROPHYLAXIS/ MAINTENANCE THERAPY

Updated guidelines on discontinuing OI prophylaxis or maintenance therapy were recently developed by the USPHS/IDSA (see sidebar, page 11). The guidelines suggest that primary prophylaxis for PCP and MAC disease and chronic suppressive therapy for CMV disease can be withdrawn in the context of CD4+ cell count increases to more than 200 cells/ μ L for PCP and more than 100 cells/ μ L for MAC and CMV. There are insufficient data to support recommendations regarding withdrawal of secondary prophylaxis

for PCP, MAC disease, and systemic fungal disease. A number of clinical trials are evaluating discontinuation of prophylaxis or maintenance therapy (Table 1, page 10). These trials may provide more definitive data on risk associated with treatment withdrawal. Patients currently having primary prophylaxis or maintenance therapy withdrawn should be closely monitored. Patients discontinuing MAC maintenance therapy should be followed for symptoms and probably do not need to be routinely followed with blood cultures in the absence of symptoms. Patients having primary PCP prophylaxis withdrawn should also be followed for signs and symptoms, as should patients

discontinuing maintenance therapy for cryptococcosis. Frequent ophthalmologic exams should be performed in those discontinuing maintenance therapy for CMV retinitis. Some practitioners are using CMV polymerase chain reaction to detect development of CMV viremia. Since *Histoplasma* antigen testing results correlate well with risk of recurrence, patients discontinuing histoplasmosis maintenance therapy should be followed by periodic testing.

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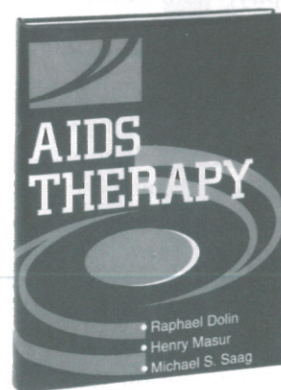
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