Reactivation of Retinal Toxoplasmosis Despite Evidence of Immune Response to Highly Active Antiretroviral Therapy

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We report a case of retinal toxoplasmosis that occurred in a patient with acquired immunodeficiency syndrome who had a previous diagnosis of cerebral toxoplasmosis, despite the patient having had a robust immune response to highly active antiretroviral therapy. Clinical decisions about whether to discontinue secondary prophylaxis for opportunistic infections continue to be challenging.

Since the introduction of highly active antiretroviral therapy (HAART), morbidity from opportunistic infections among patients with HIV has declined significantly [1]. Patients who receive HAART frequently have durable increases in CD4$^+$ lymphocyte counts as well as improvements in other indicators of immune function [2, 3]. Recent studies have supported the safety of discontinuing prophylactic therapy for several opportunistic infections [4–7].

In some cases, however, immune reconstitution is not complete, despite the occurrence of significant increases in CD4$^+$ lymphocyte counts [3]. With no standardized, clinically relevant measures to evaluate pathogen-specific immunity, it is difficult to determine whether it is safe for an individual patient to stop prophylactic measures directed against a specific opportunistic pathogen. To illustrate the risks of stopping secondary prophylactic therapy, we present a case of ocular toxoplasmosis in a patient who was receiving effective HAART.

Case report. A 36-year-old man with fever, headache, and weight loss initially presented at Duke University Medical Center (Durham, NC) for medical care in January 1999. Evaluation of the patient at that time revealed multiple ring-enhancing lesions on a CT scan of the brain and a positive HIV test result. The patient's CD4$^+$ count was 122 cells/mm^3 (6% of total lymphocytes), and he had an HIV load of 64,956 copies/mL. The results of ELISAs for the detection of *Toxoplasma* IgG and IgM were positive. The patient began receiving pyrimethamine and sulfadiazine for treatment of cerebral toxoplasmosis, and he was referred to the general medical clinic (Duke Outpatient Clinic; Durham, NC) to receive care for his HIV disease. Lamivudine, didanosine, and nelfinavir were prescribed, and the dose of pyrimethamine administered was decreased to a dose that was appropriate for secondary prophylaxis. A second CT scan of the brain that was obtained 2 months later demonstrated resolution of the brain lesions and a few residual hypodensities that were thought to denote scarring. The patient became asymptomatic.

Three months after initiation of antiretroviral therapy, the patient's CD4$^+$ count had increased to 278 cells/mm^3 (15% of total lymphocytes), and his HIV load had decreased to 13,767 copies/mL. Because virus suppression was believed to be inadequate, the patient was referred to the Duke Adult Infectious Diseases Clinic (Durham, NC), and he began receiving an experimental treatment regimen that consisted of abacavir, nevirapine, stavudine, and ritonavir/saquinavir. Six weeks after initiation of this regimen, the patient's virus load was undetectable (<400 copies/mL), and his CD4$^+$ count had increased to 419 cells/mm^3. During the next 4 months, his virus load was continuously undetectable, and his CD4$^+$ count varied (range, 353–460 cells/mm^3).

Eleven months after HIV infection was diagnosed, and after a 7-month period in which his CD4$^+$ counts were continuously >200 cells/mm^3, the patient presented at the Duke University Medical Center with blurred vision of the right eye. Ophthalmologic evaluation revealed haziness of the vitreous humor in the right eye and a subretinal lesion in the temporal periphery consistent with toxoplasmosis. Because the patient had no complaints of headache or other CNS disturbances, no imaging of the CNS was performed. The patient admitted that he had discontinued taking his medications for toxoplasmosis 3 weeks before his current presentation.

Therapy with pyrimethamine and sulfadiazine, with the ad-

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dition of clindamycin and topical corticosteroids, was reinitiated. The patient's $CD4^+$ count at the time that he presented with blurred vision was 482 cells/mm^3, and he had an undetectable HIV load. After several weeks of therapy, the visual disturbance resolved. Ophthalmologic examination was repeated, revealing improvement in the patient's condition. Treatment with clindamycin and topical corticosteroids was discontinued. The patient continued receiving secondary prophylaxis (pyrimethamine, 50 mg/day, and sulfadiazine, 1 g b.i.d.), and he was healthy at month 16 of follow-up. It was decided that prophylaxis would be continued indefinitely.

Discussion. The case that we report illustrates that although increases in T helper lymphocytes generally reflect immune reconstitution, recovery of immunity to specific pathogens is not measurable in an individual patient. Randomized, controlled trials have demonstrated that it is relatively safe to discontinue primary prophylaxis for PCP [4, 5], disseminated *Mycobacterium avium* complex [8], and cerebral toxoplasmosis [5, 6]. The data that support discontinuation of secondary prophylaxis for toxoplasmosis or cytomegalovirus infection are less conclusive [9–11]. The latest guidelines from the US Public Health Service and the Infectious Diseases Society of America state that it is "reasonable to consider" discontinuation of secondary toxoplasmosis prophylaxis if the patient (1) has completed receiving initial therapy for toxoplasmosis, (2) is asymptomatic, and (3) has demonstrated a sustained increase in the $CD4^+$ count (levels of >200 cells/mm^3 noted for $\geqslant$6 months) while receiving HAART [12]. However, this recommendation is primarily based on expert opinion, and the risk of recurrence of toxoplasmosis in patients who meet the 3 aforementioned criteria is unknown. Because fewer cases of cerebral toxoplasmosis are occurring, probably secondary to the effect of HAART, future clinical trials to define this risk appear unlikely.

Despite the uncertainty regarding discontinuation of secondary prophylaxis for opportunistic infections, patients and their clinicians are anxious to decrease the toxicity, pill burden, and expense associated with complicated medication regimens, if at all possible. The standard regimen for secondary prophylaxis for toxoplasmosis requires that 9 additional pills be added to the patient's daily regimen. However, because a recurrence of toxoplasmosis may have permanent effects on vision or cerebral function, potential harm to an individual is significant if secondary prophylaxis is stopped. Other possible approaches may include reducing the frequency of dose administration for secondary prophylaxis (e.g., reducing twice-daily administration to thrice-weekly administration) [13] as well as using alternative agents, such as trimethoprim-sulfamethoxazole and atovaquone. In any case, clinicians must carefully discuss with patients the uncertainties and risks involved, so that the most informed decisions can be made.

In summary, the present report describes a case of ocular toxoplasmosis in a patient who had a high $CD4^+$ count after receiving HAART for 11 months. This report sounds a note of caution in the swell of enthusiasm for stopping the use of prophylactic medications for HIV-infected patients with sustained $CD4^+$ count elevations. Until either reliable assays of immune function recovery for specific pathogens or more-extensive clinical data are available, we recommend that clinicians take a cautious approach in the treatment of patients with previously diagnosed toxoplasmosis and that they consider indefinite use of secondary prophylaxis, regardless of the immune response to antiretroviral therapy.

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