Highly Active Antiretroviral Therapy for HIV With Tuberculosis

Pardon the Granuloma

Highly active antiretroviral therapy (HAART) has changed the landscape of HIV infection. HIV-infected individuals are living longer, and opportunistic infections are being delayed, and in many instances patients are being liberated from prophylaxis against opportunistic infections. It has been proposed that HAART-induced restoration in the number and function of CD4 T lymphocytes is responsible for these clinical observations.

It is logical that HAART affects the natural course of tuberculosis in HIV infection because the CD4 T lymphocyte, especially the T-helper type 1 (Th1) subclass, is undoubtedly the major effector cell in cell-mediated immunity of tuberculosis. Th1 cells are characterized by their ability to produce the cytokines interferon (INF)-γ and interleukin (IL)-2, whereas T-helper type 2 (Th2) cells, another subclass of CD4+ lymphocytes, produce cytokines such as IL-4, IL-5, and IL-10. A Th1/Th2 paradigm has been proposed whereby Th1 cells secrete cytokines ("the Th1 response") that enhance immunity, whereas Th2 cells secrete cytokines ("the Th2 response") that impair immunity.

A classic example of this paradigm is leprosy. In tuberculoid leprosy, well-formed granulomas are seen and a paucity of organisms is identified. These tuberculoid lesions contain cells expressing the cytokine genes INF-γ and IL-2 and, therefore, are of the Th1 class. This in contrast to lepromatous leprosy, which is characterized by extensive skin lesions that demonstrate poorly defined lesions, abundant organisms when normal skin is stained, and cells expressing the genes of the Th2 cytokines IL-4, IL-5, and IL-10. Therefore, the Th1 cytokines promote an immunologic granulomatous response that is capable of clearing organisms, whereas the Th2 response impairs granuloma formation and immunity.

When Mycobacterium tuberculosis reaches the lower respiratory tract, the initial defense against infection is the alveolar macrophage. Once the organism is engulfed by the macrophage through a complicated process of phagocytosis, M tuberculosis can be killed by several different mechanisms involving interactions between lymphocytes and phagocytes. These cellular interactions are mediated by Th1 cytokines similar to tuberculoid leprosy.

Macrophage-lymphocyte interactions in tuberculosis involve Th1 and natural killer lymphocytes that secrete INF-γ in response to mycobacterial antigens, which activates alveolar macrophages to produce a variety of substances including reactive oxygen and nitrogen species that are involved in growth inhibition and killing of mycobacteria. Macrophages can also secrete IL-12, another Th1 cytokine, in a positive feedback loop to amplify this process.

Therefore, HAART therapy would be expected to improve immunity vs M tuberculosis by increasing the function and number of CD4+ lymphocytes, thereby augmenting the Th1 response to mycobacterial antigens and improving the granulomatous response to the organism. Although an increase in CD4+ cells might also increase lymphocytes of the Th2 class, INF-γ suppresses Th2 cell function.

In this issue of CHEST, Schluger and colleagues examine the time course of restoration of secretion of Th1 cytokines in response to mycobacterial antigens in HIV-infected individuals who began HAART. The study involved a small number of patients, but demonstrated a HAART-induced increase in proliferation of peripheral blood mononuclear cells and INF-γ in response to specific mycobacterial antigens. These increases occurred over several months and did not reach levels seen in healthy control subjects. These data suggest that HAART can improve immunity against M tuberculosis in HIV-infected individuals and heighten the granulomatous response to the organism, although it takes several months for a maximum effect and a normal level of response is not attained.

However, there is a potential downside to HAART-induced improved immunity against M tuberculosis. Although the heightened granulomatous response may help clear mycobacterial organisms, the granulomatous inflammation itself may do significant damage. Such "paradoxical reactions" have been defined as transient worsening or appearance of new signs, symptoms, or radiographic manifestations of tuberculosis that occur after initiation of treatment, and are not the result of treatment failure or a second process. In HIV-infected individuals, paradoxical reactions are common after the initiation of therapy.


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of HAART, and have been called “HAART attacks.” Paradoxical reactions may be as subtle as isolated fever or as serious as acute respiratory failure or expanding brain masses. Evidence that HAART induces paradoxical reactions is consistent with the proposed pathogenesis of restoration of the Th1 granulomatous immune response. Paradoxical responses have been shown to be more temporally related to initiation of HAART than antituberculosis therapy. Most HIV-infected patients who experience paradoxical reactions convert their tuberculin skin tests from negative to strongly positive, which is a sign of improved CD4+ cell number and function. Paradoxical reactions have been reported in 12 of 33 patients (36%) receiving HAART. Most reactions occurred within days to weeks after starting HAART, with a median of 15 days. This is more rapid than the improvement in Th1 cytokine secretion found in the group of Schluger et al, although some reports of paradoxical reactions that occur months after initiation of HAART are more consistent with their data.

Similarly, numerous cases have been reported of sarcoidosis developing in HIV-infected patients who has been started on HAART. Such patients develop thoracic adenopathy, pulmonary nodules, and reticular opacities after beginning HAART. Noncaseating granulomas consistent with sarcoidosis are found on tissue biopsy. As with the tuberculosis-treated paradoxical reactions, the sarcoidosis paradoxical reaction usually occurs with evidence of increases in CD4+ cell number induced by HAART. The pathogenesis of this condition is likely to be very similar to the paradoxical reactions seen in HAART-treated, HIV-infected pulmonary sarcoidosis patients. It is likely the antigen(s) that cause sarcoidosis are present in the HIV-infected individual with a low CD4+ count. However, CD4+ lymphocyte number and function is inadequate to mount a significant Th1-induced granulomatous response until the number and function is inadequate to mount a significant Th1-induced granulomatous response until.

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