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No Beneficial Effect of Interferon-γ Treatment in 2 Human Immunodeficiency Virus–Infected Patients with Mycobacterium avium Complex Infection

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BRIEF REPORT

Two human immunodeficiency virus–infected patients with refractory disseminated Mycobacterium avium complex infection were treated with recombinant interferon-γ (IFN-γ) given subcutaneously for 3 and 4 months, respectively. Although both patients demonstrated some clinical improvement initially, IFN-γ therapy did not produce sustained benefit.

Host defense against mycobacterial infection is critically determined by the balance between T helper type 1 (Th1) and T helper type 2 (Th2) cytokines. IFN-γ is a prototypical Th1 cytokine that is of pivotal importance for the establishment of protective immunity against mycobacteria, and studies have reported beneficial effects of IFN-γ used as an adjuvant therapeutic agent in patients with mycobacterial infections [1–5]. However, HIV-infected patients were excluded from the vast majority of these studies.

We report on the use of IFN-γ as an adjuvant therapeutic agent in 2 HIV-infected patients with refractory disseminated Mycobacterium avium complex (MAC) infection. The patients received recombinant human IFN-γ (Immukine; Boehringer Ingelheim) in an initial sc dose of 100 µg/m²; thereafter, IFN-γ, 75 µg/m², was given 3 times weekly for either 3 months (for patient 2) or 4 months (for patient 1). Similar treatment schedules previously had been found to be effective in patients with mycobacterial infections [1–4]. Both patients had received antiretroviral therapy for 17 months and antimycobacterial therapy for 15–16 months without experiencing clinical improvement. Both therapies were continued during treatment with IFN-γ.

Patient 1 was a 33-year-old man with a CD4 cell count of 50 × 10^6 cells/mL and an HIV type 1 (HIV-1) load of <1000 RNA copies/mL. He had been treated with antiretroviral therapy (most recently, with indinavir, zidovudine, and lamivudine) for 17 months. In spite of having received treatment with amikacin, clarithromycin, ciprofloxacin, ethambutol, and rifabutin, he had persistent abdominal discomfort, and cultures of feces, ascites fluid, and abdominal lymph node samples were positive for MAC. A CT scan showed massive mesenterial lymph node enlargements and ascites.

After the start of IFN-γ treatment, abdominal discomfort initially diminished. A CT scan done 1 month after initiation of IFN-γ treatment showed a slight decrease in enlargements of the mesenterial lymph node and a reduction in the amount of ascites. However, 4 months after initiation of IFN-γ treatment, the patient developed quickly progressive abdominal pain. A CT scan showed extensive lymphadenopathy (as noted previously) and an increase in the amount of ascites. IFN-γ treatment was discontinued, and the patient died of acute pulmonary edema of unknown origin several weeks later. Both directly before and during IFN-γ treatment, cultures of sputum, ascites fluid, and feces samples remained positive for MAC. The HIV load remained undetectable during IFN-γ treatment.

Patient 2 was a 31-year-old woman with a CD4 count of 1000–4000 RNA copies/mL and an HIV-1 load of <400 RNA copies/mL. She had been treated with antiretroviral agents (most recently, with ritonavir, saquinavir, lamivudine, and didanosine) for 17 months. She had disseminated MAC infection, and cultures of feces and sputum samples and of bronchoalveolar lavage fluid showed positive results, regardless of the patient having received treatment with multiple antimycobacterial drugs, including, most recently, clarithromycin, ciprofloxacin, and ethambutol. Her main complaints were persistent cough and dyspnea. A CT scan showed enlarged mediastinal lymph nodes, which resulted in occlusion of, and persistent infiltrates in, the right upper lung lobe. During the first month of IFN-γ therapy, the patient felt healthier and had less coughing and dyspnea. However, after the first month of therapy, her symptoms reappeared, and IFN-γ treatment was discontinued after 3 months. Findings of CT of the thorax were essentially un-
Production of IFN-γ (left) and IL-2 (right) by peripheral blood leukocytes obtained from 2 patients with Mycobacterium avium-intracellulare infection during IFN-γ treatment in vivo. Samples of whole blood, which were collected directly before the start of IFN-γ treatment and at monthly intervals thereafter, were diluted 1:1 in RPMI 1640 medium and were stimulated with anti-CD3/anti-CD28 (dilution, 1:1000; Central Laboratory of The Netherlands Red Cross Blood Transfusion Service, Amsterdam) for 24 h at 37°C. The cytokines were measured in supernatant by use of ELISA performed according to the instructions of the manufacturers (IFN-γ [Biosource]; IL-2 [R&D Systems]). Cytokine concentrations are expressed per milliliter of blood; expression per 1,000,000 CD4+ T cells yielded similar results (data not shown).

Overall, IFN-γ treatment had little beneficial effect for our 2 HIV-infected patients, although both patients demonstrated some clinical improvement during the first period after the initiation of IFN-γ therapy. We evaluated whether IFN-γ treatment resulted in an alteration in the balance between Th1 and Th2 cytokines in favor of protective Th1 cytokines. Samples of whole blood, obtained from the patients before the start of IFN-γ therapy and at monthly intervals thereafter, were incubated for 24 h at 37°C with the T cell stimulus anti-CD3/anti-CD28. IFN-γ treatment was not associated with an increased capacity of peripheral blood leukocytes to produce the Th1 cytokines IFN-γ and IL-2 upon stimulation (figure 1), whereas Th2 cytokine (IL-4 and IL-10) release remained low and unaltered (data not shown). These findings are in line with those from an earlier study that showed that lymphocytes from HIV-infected patients are less capable of mounting a Th1 response [5]. Our results indicate that the use of IFN-γ to treat HIV-infected patients with disseminated MAC infection may not improve the resolution of local lesions. This lack of improvement may be explained by the inability of IFN-γ to enhance the production of Th1 cytokines.

References