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Lauw, F.N.

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Chapter 8

Interferon-γ treatment has no beneficial effect during *Mycobacterium avium* complex infection in HIV-infected patients

Fanny N. Lauw,¹,² Jan T. M. van der Meer,² Jesse de Metz,³
Sven A. Danner,² and Tom van der Poll¹,²

Department of Infectious Diseases, Tropical Medicine and AIDS, the Laboratory of Experimental Internal Medicine, and the Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

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Host defense against mycobacterial infection is critically determined by the balance between T helper (Th) 1 and Th2 cytokines. Interferon-γ (IFN-γ) is a prototypic Th1 cytokine that is of pivotal importance for protective immunity against mycobacteria, and beneficial effects of IFN-γ have been reported when used as an adjuvant therapeutic agent in patients with mycobacterial infections (1-5). In the vast majority of these studies, however, HIV infected patients were excluded.

We here report on the use of IFN-γ as an adjuvant therapeutic agent in two HIV-infected patients with refractory disseminated *Mycobacterium avium* complex (MAC) infection. Patients received an initial dose of recombinant human IFN-γ (Immukine, Boehringer Ingelheim, Ingelheim/Rhein, Germany) at 100 μg/m² subcutaneously, and hereafter, IFN-γ treatment was continued at a dose of 75 μg/m² three times weekly for 3 (patient 2) or 4 months (patient 1). Similar treatment schedules previously were found effective in patients with mycobacterial infections (1-4). Both patients had received antimycobacterial therapy for 15-16 months without clinical improvement.

Patient 1 was a 33 year-old man with a CD4 count of 50 x 10⁶/mL, and a HIV-1 viral load below 1000 RNA copies/mL. He had persistent abdominal discomfort, with positive cultures for MAC in faeces, ascites fluid and abdominal lymphnodes. On CT scan, massive mesenterial lymphnode enlargements and ascites were seen. After the start of IFN-γ, the abdominal discomfort initially diminished. A CT scan 1 month after the start of IFN-γ treatment showed a slight decrease in mesenterial lymph node enlargements and a reduction in the amount of ascites. However, 4 months after the start of IFN-γ, the patient developed quickly progressive abdominal pain. A CT scan showed extensive lymph adenopathy as before and an increase in ascites. IFN-γ treatment was discontinued, and the patient died several weeks later due to acute pulmonary edema of unknown origin. The HIV load remained undetectable during IFN-γ treatment.

Patient 2 was a 31-year-old woman with a CD4 count of 140 x 10⁶/mL and a HIV-1 viral load below 400 RNA copies/mL. She had disseminated MAC infection with positive cultures in feces, sputum and bronchoalveolar lavage fluid. Her main complaints were persistent coughing 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 better, with less coughing and dyspnea. However, thereafter her symptoms re-appeared, and IFN-γ was discontinued after 3 months. Her CT-thorax was essentially unchanged at that time. The HIV load remained undetectable.

Overall IFN-γ treatment had little beneficial effect in our two HIV infected patients, although both patients demonstrated some clinical improvement in 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 type cytokines in favor of protective Th1 cytokines.
Whole blood, obtained from the patients before the start of IFN-γ therapy and at monthly intervals thereafter, was 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 interleukin (IL)-2 upon stimulation (Fig. 1), while Th2 cytokine (IL-4, IL-10) release remained low and unaltered (data not shown). These findings are in line with earlier studies showing that lymphocytes from HIV infected patients are less capable of mounting a Th1 response (5). Our results indicate that IFN-γ treatment in HIV-infected patients with disseminated MAC infection may not be capable of improving the resolution of local lesions. This may be explained by the inability of IFN-γ to enhance the production of Th1 type cytokines.

![Figure 1](image-url)

**Figure 1.** Production of IFN-γ and IL-2 by peripheral blood leukocytes from patients with MAC infection during IFN-γ treatment in vivo. Whole blood, collected directly before the start of IFN-γ treatment, and at monthly intervals thereafter, was diluted 1:1 in RPMI and stimulated for 24 h at 37°C anti-CD3/anti-CD28 (CLB, Amsterdam, the Netherlands; 1:1000). Cytokines were measured in supernatant by ELISA according to the instructions of the manufacturers (TNF: Biosource, Fleurus, Belgium; IL-2: R&D Systems, Abingdon, UK). Cytokine concentrations are expressed per mL blood; expression per $10^6$ CD4+ T cells yielded similar results (data not shown).

**References**


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