Gamma-interferon treatment for resistant oropharyngeal candidiasis in an HIV-positive patient

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Sir,

Oropharyngeal candidiasis (OPC) is the most common opportunistic infection occurring in HIV-infected individuals. Infection is often recurrent, requiring long-term prophy- lactic antifungal therapy. Azole resistance is a problem, and the molecular mechanism has recently been discussed by Martinez et al.1

We report anecdotal evidence of the efficacy of subcutaneous interferon-γ (IFN-γ) in an immunosuppressed patient with drug-resistant oropharyngeal candidiasis and advanced HIV disease. A 31-year-old male patient, diagnosed as HIV positive in 1992, first experienced OPC in 1993 and was treated successfully with oral fluconazole (200 mg/day for 7 days).

In 1994 the patient experienced several recurrent episodes of OPC, which were treated with oral fluconazole (200–400 mg/day for 7–14 days). He was not adherent to antiretroviral therapy, despite worsening immunosuppression (CD4+ count <100 cells/mm3). Oral fluconazole 50 mg daily was commenced as prophylactic therapy for OPC. Further recurrences of OPC were treated with oralitraconazole (200 mg twice daily for 21 days) and ketoconazole (200 mg once daily for 14 days) with only partial resolution of symptoms.

The patient was admitted to hospital in September 1998 with profound bone marrow hypoplasia secondary to Mycobacterium avium (MAC) infection (treated with clarithromycin, rifampicin and ethambutol). He was highly antiretroviral drug experienced, and his antiretroviral regime at time of presenta- tion was abacavir, lamivudine and stavudine. CD4+ count was 7 cells/mm³ and viral load was 48 000 copies/mL. He continued to have OPC that did not respond to treatment with topical nystatin and amphotericin, and that was found to be clinically and microbiologically resistant to azole antifungals [Candida albicans; fluconazole MIC > 128 mg/L and itraconazole MIC > 16 mg/L; a pre-treatment isolate of C. albicans was susceptible to fluconazole (MIC 2 mg/L) and itraconazole (0.5 mg/L)]. The patient refused intravenous therapy with amphotericin B.

It was therefore decided to stimulate macrophage function with IFN-γ 1 mg three times weekly, administered subcutaneously, and to continue topical amphotericin and nystatin.

Within 3 weeks of commencing this therapy there was a dramatic improvement in symptoms and signs of OPC. IFN-γ was discontinued after 4 months of treatment, and within 4 days there was recurrence of his symptoms. IFN-γ was therefore reintroduced successfully.

IFN-γ (a T cell-derived lymphokine) is a broadly acting host defence-enhancing cytokine. Candida infection may be associated with an insufficient IFN-γ response of the host and it has been demonstrated that peripheral blood mononuclear cells from HIV-infected patients show decreased ability for proliferative and differentiative cytotoxic responses (including the production of IFN-γ) to candidal proteins.2 IFN-γ has antineoplastic effects and indirect antifungal and antiviral activity mediated by immunomodulatory effects. At a cellular level these include macrophage activation, stimulation of antigen presentation through class I and class II major histocompatibility complex molecules, regulation of leucocyte-endothelium interaction, and effects on cell proliferation and apoptosis.3

IFN-γ has been demonstrated to have synergic activity with amphotericin B against intracellular Cryptococcus neoformans in animal studies.5

The proposed mechanisms by which IFN-γ exerts an antifungal effect are by increasing production of reactive oxygen radicals, which increases the candidical activity of granulo- cytes, and by inhibition of phagocytosis. In vitro studies have demonstrated that IFN-γ can reduce endothelial cell phagocytosis by 41.3% compared with untreated endothelial cells.6

As yet there have been no reported clinical trials of IFN-γ in HIV-infected patients with azole-resistant OPC. These patients (such as the patient described above and the patient described by Martinez et al.1) may benefit from the use of immunological therapy such as IFN-γ in combination with antifungal therapy.
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References


