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Antiviral Research 29 (1996) 105–109

Antiviral Research

Short communication

Consensus symposium on combined antiviral therapy; Overview of interferon and IL-2 combinations for the treatment of HIV infection

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Abstract

Among the immunomodulatory cytokines that have been evaluated for the treatment of HIV disease, α-interferon and interleukin-2 (IL-2) have been the most extensively studied. Monotherapy with α-interferon is effective therapy for HIV-associated Kaposi's sarcoma (KS) in patients with CD4 counts >150 cells/mm^3. However, the doses necessary to achieve a significant anti-tumor effect are often poorly tolerated. Combination therapy with α-interferon and zidovudine is associated with dose-limiting toxicities and an anti-tumor effect similar to that of higher dose α-interferon monotherapy. The combination of α-interferon and zidovudine can synergistically inhibit HIV replication in vitro; however, in vivo results suggest the anti-HIV effect of this combination is no greater than that seen with zidovudine monotherapy. Whether combination of interferon-α and other antiviral drugs will be useful in the treatment of HIV infection remains to be seen. Recent studies employing intermittent courses of IL-2 combined with continuous antiretroviral therapy indicate that sustained rises in CD4 counts can be achieved. The ability of IL-2 therapy to result in a sustained rise in CD4 counts is critically dependent on the pre-treatment CD4 count. The immunologic and clinical significance of these IL-2-induced increases in CD4 counts is unknown. Larger, controlled trials are currently underway to evaluate the role of intermittent IL-2 therapy in HIV infection.

Keywords: Alpha-interferon; Interleukin-2; HIV; Cytokine

1. Introduction

A variety of cytokines have been evaluated as potential therapeutic agents in patients infected with HIV. Among them, the interferons, interleukin-2 (IL-2), and the colony stimulating factors (G-CSF, GM-CSF) have received the most attention. Although the colony stimulating factors are effective in augmenting neutrophil number and function, they have no role in the primary treatment of HIV infection. This paper will focus on the roles of interferons and IL-2 in the treatment of HIV infection.

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SSDI 0166-3542(95)00930-K

2. Interferons

2.1. Interferon-α

Even before the AIDS epidemic, interferon-α was known to exhibit antiretroviral activity. With the identification of HIV as the cause of AIDS, several laboratories began to examine the effects of interferon-α on HIV replication. It was initially shown that concentrations of interferon-α in the range of 100 U/ml could suppress HIV replication in tissue culture (Ho et al., 1985). This effect was most pronounced when interferon-α was continually present in the culture media and comparable in magnitude to the level of suppression seen with zidovudine. Subsequent work demonstrated that inhibition of HIV replication was more pronounced for class I interferons than with interferon-γ (Yamada et al., 1988). At the molecular level, interferon-α appears capable of inhibiting multiple steps in the HIV life cycle, including pre-integration events, de novo transcription, post-transcriptional events, and the assembly and release of progeny virus (Shirazi and Pitha, 1992; Francis et al., 1992; Ho et al., 1985).

The first therapeutic trials of interferon-α in HIV disease focused on the treatment of Kapsoi's sarcoma (KS). In these studies, interferon-α in doses of approximately 30–35 million units/day demonstrated significant antitumor effect, with response rates of 20–67% (reviewed in Sneller and Lane, 1993). An important finding of these studies was the strong correlation between clinical response and the level of immune competence, as measured by CD4% or absolute CD4 T cell number. These results suggest that interferon-α is acting as a biological response modifier to mediate its antitumor effect.

In addition to the anti-tumor effect, these studies provided evidence that interferon-α also had an antiretroviral effect. Like the antitumor effect, this anti-HIV effect was strongly correlated with the level of immune competence, again suggesting that, in vivo, interferon-α was acting to enhance the immune response rather than having direct antiviral activity.

To better assess the antiretroviral activity of interferon-α, a randomized, placebo-controlled trial in asymptomatic HIV-infected individuals with CD4 counts >400 cells/mm^3 and positive cultures for HIV was carried out (Lane et al., 1990). Of the 17 patients randomized to interferon-α treatment, seven (41%) developed persistently negative cultures for HIV, while only two of 17 patients randomized to placebo became culture negative. During the treatment period, CD4 percentages remained stable or increased in patients receiving interferon-α and declined slightly in patients receiving placebo. Toxicity associated with interferon-α treatment was substantial as indicated by the fact that 35% of patients randomized to interferon-α withdrew from the study because of toxicity. The most prominent toxicities were flu-like symptoms, neutropenia and elevations of hepatic transaminases (Lane et al., 1990). The results of this trial suggest that, although it is associated with considerable toxicity, interferon-α may exhibit some antiretroviral activity in patients with >400 CD4 cells/mm^3.

Combination therapy with zidovudine and interferon-α has been evaluated for the treatment of HIV-associated KS (Kovacs et al., 1989; Fischl et al., 1991). Co-administration of interferon-α and zidovudine is associated with a high frequency of certain toxicities (neutropenia, thrombocytopenia, and transaminase elevations) that are dose limiting. The maximum tolerated dose of interferon-α is between 4–10 million units/day depending on the zidovudine dose (Kovacs et al., 1989; Fischl et al., 1991). At these doses of interferon-α, the anti-KS effect seen with combination therapy is equivalent to that observed with higher dose interferon-α monotherapy. The combination of zidovudine and interferon-α also appeared to have anti-HIV activity in KS patients with higher CD4 counts (Kovacs et al., 1989). These findings, plus the fact that zidovudine and interferon-α can act synergistically to inhibit HIV replication in vitro (Jonhson et al., 1990), led to clinical trials of combination therapy with these two agents in HIV-infected patients. To date, trials of zidovudine and interferon-α combination therapy have failed to show a clinically significant anti-HIV effect beyond that achieved with zidovudine monotherapy (Edlin et al., 1992; Jos Frissen et al., 1994). Whether combination of interferon-α and

other antiviral drugs will be useful in the treatment of HIV infection remains to be seen.

2.2. Interferon-γ

Unlike interferon-α, interferon-γ has minimal antiretroviral activity in vitro and, in some systems, can up-regulate HIV expression. Administration of interferon-γ to patients with HIV-associated KS has shown no apparent clinical benefit. However, interferon-γ is a potent macrophage activator and may have a role as adjunctive therapy in the treatment of certain opportunistic infections.

3. Interleukin-2

Interleukin-2 (IL-2) is a glycoprotein produced by activated T lymphocytes that enhances the proliferation and differentiation of natural killer (NK) cells, T lymphocytes, and B lymphocytes. The rational for the use of IL-2 in the treatment of HIV infection comes from in vitro observations that IL-2 can enhance proliferation of peripheral blood T cells from HIV-infected individuals. In addition, NK activity, which is also depressed in HIV infection, can be restored by the incubation of peripheral blood mononuclear cells with IL-2. These in vitro studies suggested that it might be possible to restore some degree of immune competence in vivo by treatment of HIV-infected patients with IL-2.

Early trials of IL-2 therapy in AIDS and ARC patients met with little success (reviewed in Sneller and Lane, 1993). Because of marked variations in the doses, length of treatment and route of administration, it is difficult to compare the results of these trials. Nevertheless, no clinical benefits could be demonstrated in these studies and only transient changes in lymphocyte counts were observed.

The minimal immunologic changes seen with IL-2 monotherapy, along with concerns that IL-2 induced T lymphocyte activation could lead to increased HIV replication and dissemination, led to a number of trials of IL-2 combined with zidovudine (Table 1). Continuous intravenous infusion of IL-2 at doses in the range of $1.5–12 \times 10^6$ IU/ m^2/ day resulted in transient changes in CD4 counts and NK activity in patients with CD4 counts $\geq 400/mm^3$ (Schwartz et al., 1991). In a follow-up study (Wood et al., 1993), 19 HIV-infected patients were treated with zidovudine combined with polyethylene glycol-conjugated IL-2 (PEG-IL-2). PEG -IL-2 has a prolonged half life and was administered intravenously once a week. Acute dose related increases in CD4 counts, HIV-specific cytotoxicity, and NK activity were seen. No increases in p24 antigenemia or HIV DNA (as detected by polymerase chain reaction) were seen in this study (Wood et al., 1993). The maximum tolerated dose of IL-2 in this study was 3×10^6 IU/m^2 with adverse reactions of hypotension, neutropenia and neurotoxicity. Similar results were obtained when IL-2 ($0.2–2 \times 10^6$ IU/ m^2/day) or PEG -IL-2 (up to 1×10^6 IU/week) was administered by subcutaneous injection (McMahon et al., 1994; Waites et al., 1992). Administration of zidovudine combined with low doses of PEG-IL-2 (36 000 IU/week) given by subcutaneous injection to patients with CD4 counts $>100/mm^3$ resulted in insignificant changes in CD4 counts and quantitative HIV cultures. Small but statistically significant increases in NK activity were detected (Teppler et al., 1993a; Teppler et al., 1993b). Taken together, these studies indicate that administration of IL-2 or PEG-IL-2 combined with zidovudine results in transient immunologic changes and is associated with significant, dose limiting toxicities.

Sustained rises in CD4 counts have been reported in HIV-infected patients treated with antiretrovirals combined with intermittent IL-2 therapy (Kovacs et al., 1995). In this study, IL-2 was given at doses of 12–18 MIU/d for 5 days every 8 weeks. In 6 of 10 patients with baseline CD4 counts higher than 200 cells/μl, intermittent IL-2 therapy was associated with at least a 50% increase in the number of CD4 cells. A decline in the percentage of CD8 cells that expressed HLA-DR was also seen. Four patients had a transient but consistent rise in plasma HIV RNA at the end of each IL-2 infusion. In patients with baseline CD4 counts less than 200 cells/μl, IL-2 therapy was associated with increased viral activation, few immunologic improvements and substantial toxic-

Table 1
Summary of IL-2+ antiviral trials

Study	No. patients	CD4 count	Dose (IU)	Immunologic effects	Effect on viral load
Schwartz et al., 1991	10	>400	IV; 1.5-12 × 10^6/M2 5d/week for 3 weeks	Increase in CD4 count Increase in NK function	No increase in p24
Waites et al., 1992	25	>200	SC; PEG 0.05-1 × 10^6	Transient increase in CD4 count	No increase in p24
	25	<200	2 of 4 week × 28 weeks	Only in >200 group	
Wood et al., 1993	19	>400	IV; PEG 1-5 × 10^6	Acute increase in CD4 count	No increase in p24 or HIV by DNA PCR
		200-400	Weekly × 25 weeks	Increase in NK function	
		<200			PCR
Teppler et al., 1993a	16	>100	ID; PEG 3.6 × 10^4/week	Increased NK function	No increase in quantitative viral cultures
Teppler et al., 1993b			× 4 months	Increased DTH recall	
McMahon et al., 1994	16	AIDS/ARC	SC; 0.2-2.0 × 10^6 Daily × 5 days	Increase in CD4 count Increase in NK function	No increase in p24
Kovacs et al., 1995	25	>200	IV; 6-18 × 10^6/d for 5	Sustained increases in CD4	Transient increases in bDNA in >200; sustained increases in bDNA in <200
		<200	Days every 8 weeks	Counts only in >200 group	

Key: IV, intravenous; ID, intradermal; SC, subcutaneous; PEG, polyethylene glycol conjugated IL2; PCR, polymerase chain reaction; DTH, delayed-type hypersensitivity; 400 IU, 1 μg of IL2; 70 kg human, 1.8 M^2.

ity. The results of this study indicate that intermittent courses of IL-2 can improve some of the immunologic abnormalities associated with HIV infection in patients with CD4 counts higher than 200 cells/μl. The immunologic and clinical significance of these sustained increases in CD4 counts is unknown. Larger, controlled trials are currently underway to evaluate the role of intermittent IL-2 therapy in HIV infection.

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