

INCREASES IN CD4 T LYMPHOCYTES WITH INTERMITTENT COURSES OF INTERLEUKIN-2 IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

A Preliminary Study

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Abstract Background. Interleukin-2 is an important regulatory cytokine of the immune system, with potent effects on T cells, B cells, and natural killer cells. In vitro, interleukin-2 can induce the proliferation and differentiation of peripheral-blood mononuclear cells from patients infected with the human immunodeficiency virus (HIV).

Methods. We treated 25 HIV-infected patients with interleukin-2 administered as a continuous infusion at a dosage of 6 to 18 million IU per day for 5 days every 8 weeks during a period of 7 to 25 months. All patients also received at least one approved antiviral agent. Immunologic and virologic variables were monitored monthly.

Results. In 6 of 10 patients with base-line CD4 counts higher than 200 per cubic millimeter, interleukin-2 therapy was associated with at least a 50 percent increase in the number of CD4 cells. Changes ranged from -81 to

+2211 cells per cubic millimeter. Interleukin-2 therapy resulted in a decline in the percentage of CD8 lymphocytes expressing HLA-DR and an increase in the percentage of CD4 lymphocytes that were positive for the p55 chain of the interleukin-2 receptor. Four patients had a transient but consistent increase in the plasma HIV RNA level at the end of each infusion. In the remaining 15 patients, who had CD4 counts of 200 or fewer cells per cubic millimeter, interleukin-2 therapy was associated with increased viral activation, few immunologic improvements, and substantial toxic effects.

Conclusions. Intermittent courses of interleukin-2 can improve some of the immunologic abnormalities associated with HIV infection in patients with more than 200 CD4 cells per cubic millimeter. (N Engl J Med 1995;332:567-75.)

RESTORATION and preservation of the immune system are crucial elements in the successful clinical management of human immunodeficiency virus (HIV) infection. Current therapy for HIV infection relies primarily on the administration of antiretroviral nucleoside analogues, either alone or in combination.¹⁻⁵ Although these drugs have a clinical benefit, it is temporary and most apparent in advanced stages of infection. None of the currently licensed drugs prevent the immunologic deterioration associated with HIV infection. Attempts to reconstitute the immune system have used bone marrow transplantation and lymphocyte transfers,⁶ potential immunomodulating agents such as ditiocarb sodium⁷ and inosine pranobex,⁸ and recombinant cytokines such as interferon alfa,⁹ interferon gamma,¹⁰ and interleukin-2.¹¹⁻¹⁸

A T-cell-derived lymphokine with several immunomodulating effects, interleukin-2 is capable of inducing the activation, proliferation, and differentiation of both T and B lymphocytes.¹⁸ In vitro studies have shown that exogenous interleukin-2 increases the depressed natural-killer-cell activity and cytomegalovirus-specific cytotoxic effect of peripheral-blood mononuclear cells from patients with the acquired immunodeficiency syndrome.¹⁹ These findings provide a rationale for evaluating the role of interleukin-2 in restoring immune

function in HIV-infected patients, and clinical trials of both native and recombinant interleukin-2 have been in progress since 1983.¹¹⁻¹⁸

In initial trials using native and recombinant interleukin-2, we demonstrated that a three-to-eight-week course of interleukin-2 administered by continuous infusion was well tolerated at dosages of up to 12 million IU per day and was associated with transient increases in CD4 counts. Bone marrow-biopsy specimens obtained after the completion of interleukin-2 therapy had more normal lymphocytes than specimens obtained before therapy, suggesting that the effect of interleukin-2 could not be explained simply by the shifting of lymphocytes to the peripheral blood.

We undertook the current study to evaluate intermittent courses of interleukin-2 for the long-term management of HIV infection. We initially focused on HIV-infected patients with a moderate suppression of the immune system (CD4 counts higher than 200 per cubic millimeter), on the basis of earlier work demonstrating that such patients are more likely to have a response to immunomodulators than patients with severely impaired immune function.^{9,20}

METHODS

Patients were eligible for enrollment if they had HIV infection and no concurrent opportunistic infections. The study was approved by the institutional review board of the National Institute of Allergy and Infectious Diseases, and all patients provided written informed consent after the risks associated with participation in the study had been explained to them.

The study was conducted in two parts. The first part was a dose-escalation trial in which 23 patients with CD4 counts higher than 200 per cubic millimeter received, as inpatients, a single 21-day or 5-day course of recombinant interleukin-2 diluted in 500 ml of 5 percent dextrose in water (Chiron, Emeryville, Calif.) and administered by continuous infusion through a central line, at dosages ranging from

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Dr. Lane and Dr. Kovacs have a pending patent application related to the research reported in this article.

1.8 million to 24 million IU per day. All patients received zidovudine (100 to 200 mg five times a day or every four hours) beginning at least six weeks before the first course of interleukin-2.

In the second part of the study, 10 patients with CD4 counts higher than 200 per cubic millimeter received a five-day course of interleukin-2 by continuous infusion, initially at a dose of 18 million IU per day, every eight weeks. Because of the concern that interleukin-2 could lead to increased HIV replication, antiretroviral agents were administered concomitantly, with most patients receiving zidovudine

(100 mg five times per day). As other antiretroviral agents became available, their use was also allowed in consultation with the referring physician.

Subsequently, 15 patients with CD4 counts equal to or less than 200 per cubic millimeter were enrolled to examine the potential benefit of interleukin-2 in combination with any approved antiretroviral agent (zidovudine, didanosine, or zalcitabine alone or in combination) in patients with lower CD4 counts.

Interleukin-2 was administered through either a central or a pe-

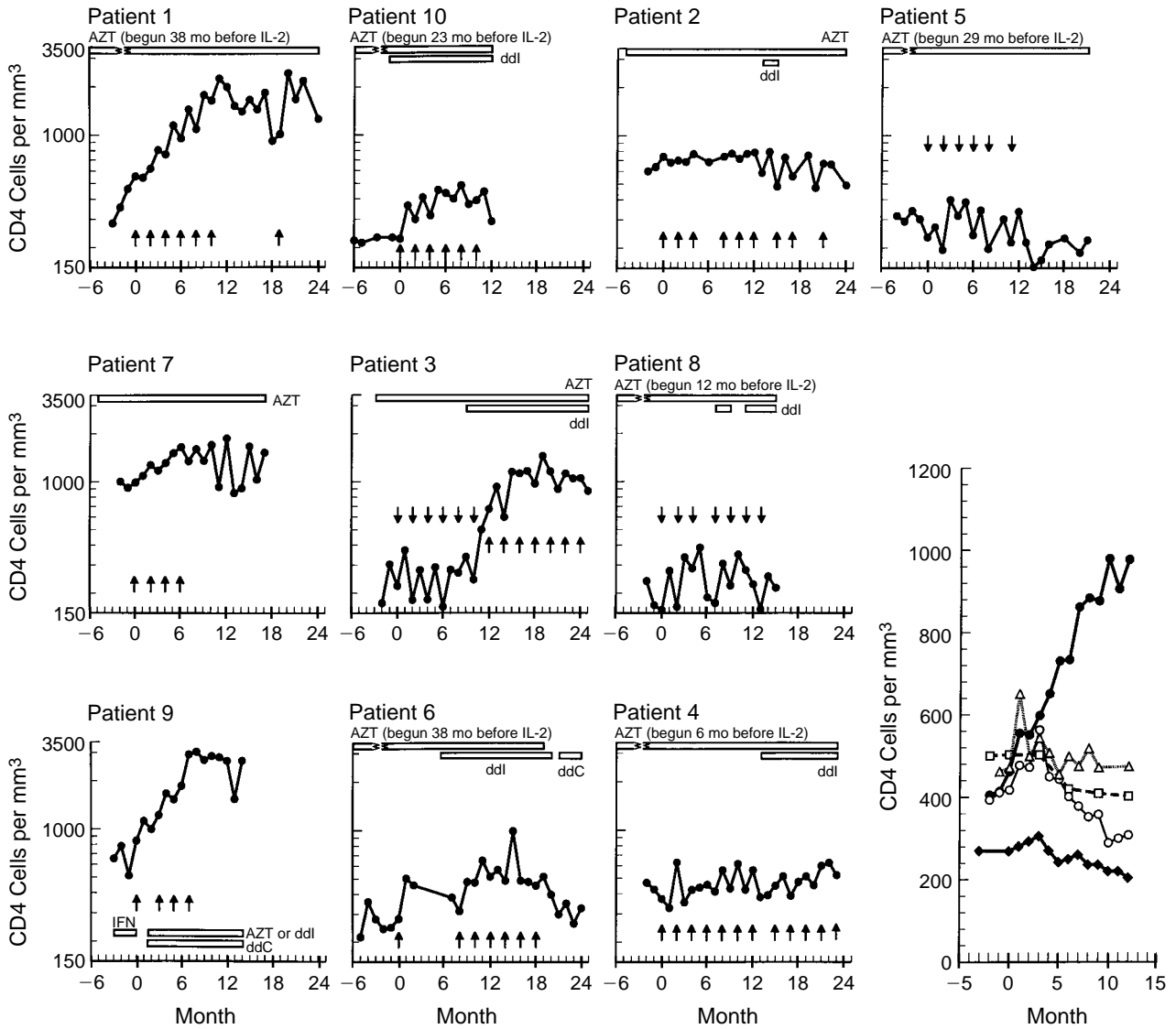


Figure 1. Changes in CD4 Counts during Intermittent Courses of Recombinant Interleukin-2 in 10 Patients with Initial Counts Higher Than 200 per Cubic Millimeter.

Antiretroviral therapy is indicated by the horizontal bars. The six patients at the left had the better responses. The arrows denote courses of interleukin-2 therapy; CD4 counts at those points in time were determined before the administration of interleukin-2. Patient 9 received a single course of interleukin-2 in combination with interferon alfa as part of a phase 1 evaluation of that combination.¹⁷ Patient 5 received six additional courses of interleukin-2 from months 20 to 30, with no increase in the CD4 count. Patients 1, 7, 9, and 10 had undetectable levels of HIV RNA before therapy. In Patient 3 viral RNA dropped to undetectable levels after the initiation of didanosine. The lower right-hand panel compares mean CD4 counts during one year in the 10 patients (solid circles) with mean CD4 counts in four groups of subjects enrolled in studies conducted by the National Institute of Allergy and Infectious Diseases: 12 controls matched for the CD4 count and treated only with zidovudine (open circles),²⁹ 25 patients with CD4 counts higher than 200 per cubic millimeter who were treated for the first time with didanosine plus interferon alfa-2b for one year (triangles), 20 patients treated with zidovudine and selected from a cohort of 180 patients on the basis of the duration of prior zidovudine therapy and the CD4 count (squares), and 10 patients with CD4 counts higher than 200 per cubic millimeter who were treated with zidovudine plus didanosine for a minimum of six months, with subsequent adjustments in therapy allowed if the CD4 count fell to less than 25 percent of the baseline value (diamonds). A log scale is used for the individual graphs, and a linear scale for the comparison graph. AZT denotes zidovudine, IL-2 interleukin-2, ddl didanosine, IFN interferon, and ddC zalcitabine.

ripheral line. For peripheral infusions, the interleukin-2 was placed in a solution of 5 percent dextrose in water containing 0.1 percent albumin. Treatment was permitted with acetaminophen, ibuprofen, antiemetic agents, antidiarrheal agents, meperidine, and anxiolytic agents as needed for the relief of side effects. Immunologic, virologic, and safety variables were examined immediately before, one day after, and one month after each round of interleukin-2. The dose was reduced by increments of 6 million IU for serious side effects.

Determinations of lymphocyte subgroups and surface markers were performed by one-color or two-color flow cytometry with monoclonal antibodies.²¹ Levels of p24 antigen were determined by an immune-complex-dissociated assay (Coulter, Hialeah, Fla.).²² Plasma HIV cultures were performed as previously described.²³ Particle-associated plasma HIV RNA levels were determined with the branched-DNA signal-amplification assay (Chiron).²⁴⁻²⁶

RESULTS

Dose-Escalation Study

Twenty-three patients were enrolled in the dose-escalation study. The maximal tolerated dosage of interleukin-2 used in combination with zidovudine was 12 million IU per day when administered for 21 days and 18 million IU per day when administered for 5 days. Dose-limiting side effects, which were similar to those previously associated with interleukin-2 therapy alone,^{27,28} included capillary leak, severe influenza-like symptoms, hepatic and renal dysfunction, thrombocytopenia, and neutropenia. There were transient changes in CD4 counts during this phase, but no consistent long-term changes in immunologic variables (data not shown). No consistent changes in p24 antigen levels or HIV cultures from peripheral-blood mononuclear cells were found.

Patients with High CD4 Counts

To examine the long-term effects of repeated courses of interleukin-2 with concomitant antiretroviral therapy, 10 patients (8 men and 2 women, ranging in age from 29 to 45 years) received a five-day course of interleukin-2 by continuous infusion every eight weeks (Fig. 1). These patients received a total of 4 to 13 courses of interleukin-2, and follow-up ranged from 22 to 40 months. The initial dosage was 18 million IU per day. Eight patients required a reduction in the dosage to 12 million IU per day (Patients 1, 2, 4, 6, 8, and 10) or 6 million IU per day (Patients 7 and 9), primarily because of fever and severe influenza-like symptoms. Table 1 shows the incidence of side effects. Patients 2 and 7 chose to discontinue interleukin-2 therapy after four and nine courses, respectively, but continued to be followed.

In 6 of the 10 patients, the CD4 count was increased by more than 50 percent one and two months after a course of interleukin-2 (Fig. 1 and 2). We next determined whether the interleukin-2-induced increase in the CD4 count resulted from a monoclonal, oligoclonal, or polyclonal expansion of cells. In three patients the proportions of CD4 T cells expressing different subgroups of T-cell receptors were measured by a two-color fluorescence-activated cell-sorter (FACS) analysis with monoclonal antibodies specific for different variable regions of the β chain ($V\beta$) of the T-cell receptor. In all cases there was a polyclonal increase in

Table 1. Toxic Effects during Intermittent Therapy with Interleukin-2 in 10 Patients with HIV Infection.*

TOXIC EFFECT	INCIDENCE (%)
Clinical side effects	
Rash†	79
Fatigue or malaise	76
Myalgias or arthralgias	61
Nausea	59
Capillary leak‡	57
Temperature >39°C§	57
Diarrhea	35
Headache	35
Aphthous ulcers or stomatitis	32
Nasal or sinus congestion	31
Abdominal pain¶	21
Altered perception	13
Depression	5
Other	5
Laboratory abnormalities	
Calcium <2.0 mmol/liter**	57
Albumin <3.0 g/dl	37
Magnesium <0.60 mmol/liter	37
Sodium <130 mmol/liter	17
Platelets <75,000/mm ³	8
Hemoglobin <10 g/dl	7
Alkaline phosphatase >500 U/liter	5
Other††	4

*The 10 patients received a total of 75 courses of interleukin-2: 31 courses at 18 million IU per day, 41 courses at 12 million IU per day, and 3 courses at 6 million IU per day.

†Predominantly diffuse erythroderma or seborrheic dermatitis, with four episodes of dyshidrosis.

‡Defined as a gain in weight ≥ 2 kg; often associated with decreased urinary output, low blood pressure, and edema.

§Often associated with chills and rigors.

¶Includes two cases of sonographically documented acalculous cholecystitis.

||Hypothyroidism (thyroid-stimulating hormone >10 mU per liter) in two patients, fasting hyperglycemia (glucose >150 mg per deciliter [8.33 mmol per liter]) in two patients, and nodular regenerative hyperplasia of the liver and esophageal varices in one patient with chronic hepatitis B.

**Associated with tetany on one occasion.

††Three episodes of neutropenia (<1000 cells per cubic millimeter), and one episode of a creatinine elevation above 3.0 mg per deciliter (265 μ mol per liter).

CD4 cells (Fig. 3). Changes in the CD8 count were not necessarily concordant with changes in the CD4 count (Fig. 2). For the most part, CD8 counts remained stable.

The percentage of lymphocytes that were positive for HLA-DR was elevated (≥ 15 percent) in all 10 patients before the study (Fig. 2). During treatment with interleukin-2, the proportion of cells that were positive for HLA-DR was reduced by at least 25 percent in seven of the patients (Fig. 2). A similar decline was seen in cells that were positive for CD38 (another marker of cell activation) in the two patients for whom serial measurements were available (data not shown). The proportion of cells that were positive for the α chain of the interleukin-2 receptor p55 (CD25) increased progressively in nine patients (Fig. 2). An increased level of CD25 expression immediately before a course of interleukin-2 appeared to be correlated with an increase in the CD4 count afterward.

A two-color FACS analysis showed that CD8-positive cells were the predominant population of cells that were positive for HLA-DR before the study and were the primary population accounting for the decline in

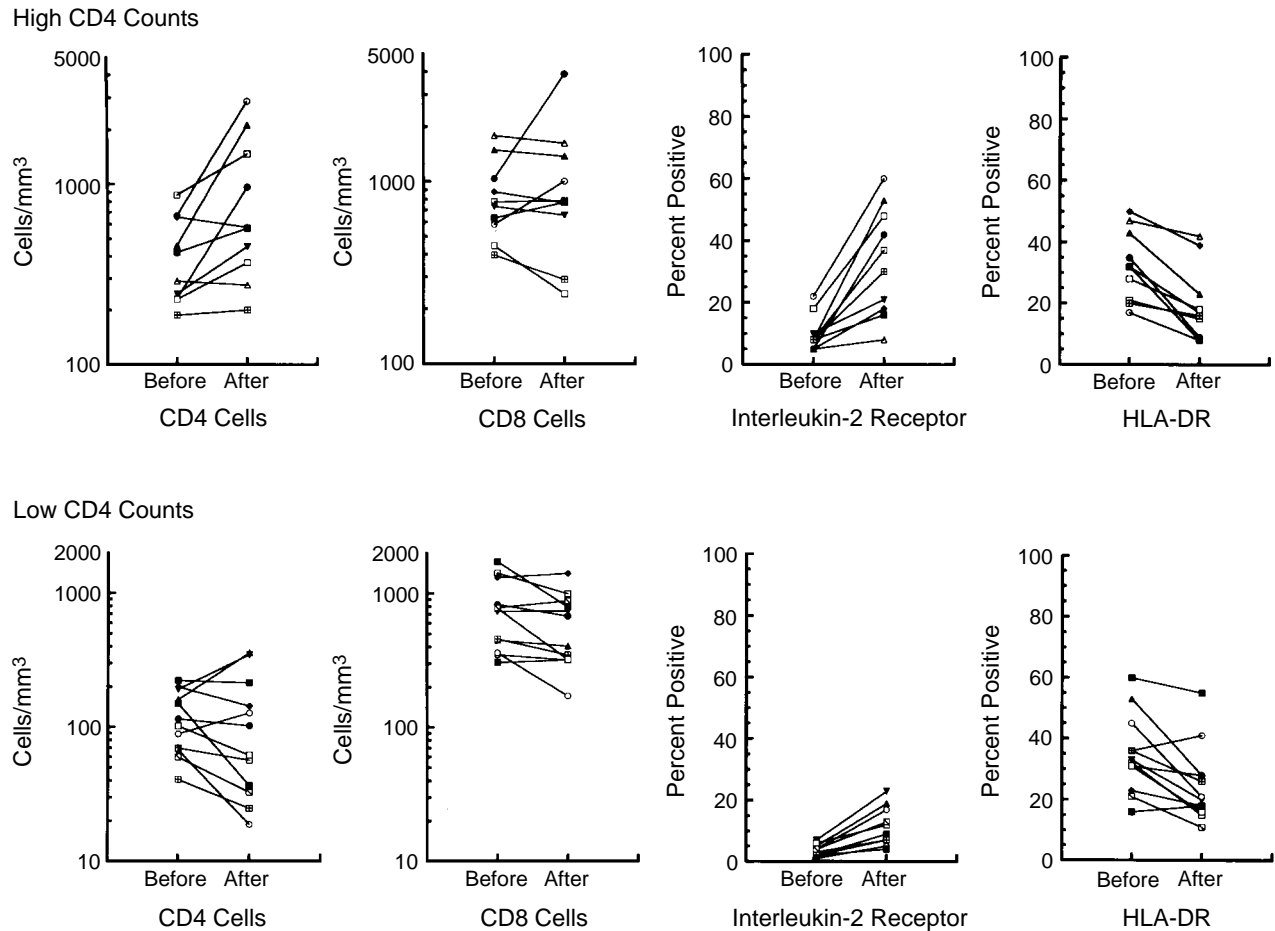


Figure 2. Changes in CD4 and CD8 Counts and in the Expression of the Interleukin-2 Receptor (CD25) and HLA-DR during Intermittent Courses of Recombinant Interleukin-2 in the 10 Patients with High CD4 Counts (>200 per Cubic Millimeter) and the 12 Patients with Low CD4 Counts (\leq 200 per Cubic Millimeter) Who Could Be Evaluated.

Values before interleukin-2 treatment are the means of three values before the first course of interleukin-2, and values after interleukin-2 treatment are the means of the values one and two months after the latest course of interleukin-2. The same symbol is used for each patient in each panel.

this marker after therapy (Fig. 4). The increase in the expression of the interleukin-2 receptor during therapy with interleukin-2 was predominantly due to an increase on CD4-positive cells (Fig. 4).

Since HIV replicates in activated cells, a primary concern with the use of interleukin-2 in HIV-infected patients is that the viral burden will be increased. No consistent changes in the overall viral load in the peripheral blood, as evaluated by serial measurement of p24 antigen (Fig. 5) or plasma viremia (data not shown), were detected during multiple courses of interleukin-2 therapy. One patient had a gradual decline, and two a gradual increase, in p24 antigen levels during one year of therapy. In the other seven patients, p24 antigen levels were consistently low or undetectable.

Because p24 antigen levels do not appear to be sensitive to acute changes in the plasma viral burden, we measured HIV RNA with the branched-DNA assay in frozen plasma from nine patients (Fig. 5B). In four patients, a consistent increase in particle-associated HIV RNA was noted immediately after the completion of a

course of interleukin-2; this increase was not associated with an increase in p24 antigen levels and was almost always transient, with a return to the base-line value by the next follow-up visit. HIV RNA was undetectable throughout therapy in four patients and showed no consistent increase in one.

Pneumocystis carinii pneumonia developed eight and nine months after the last course of interleukin-2 in Patients 2 and 5, respectively, neither of whom had an increase in CD4 counts with interleukin-2 therapy. The infections occurred with viral burdens of 555,000 and 435,000 copies of HIV RNA per milliliter and CD4 cell counts of 400 and 31 cells per cubic millimeter, respectively. Opportunistic infections did not develop in any of the other patients.

Patients with Low CD4 Counts

Fifteen patients with 200 or fewer CD4 cells per cubic millimeter were subsequently enrolled in the study. Twelve of the patients received two to five courses of interleukin-2. The side effects were more severe in this group of patients than in the group with higher CD4

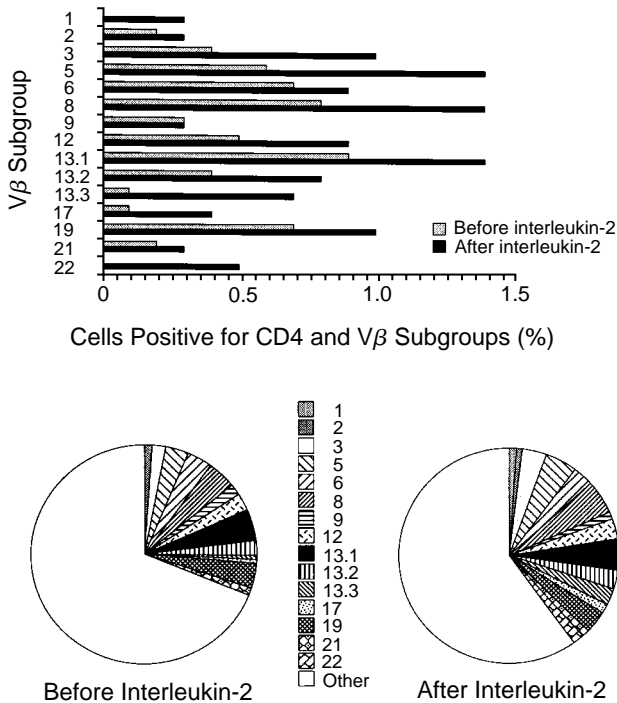


Figure 3. Changes in V β Subgroups in Patient 1 before and 10 Months after Six Courses of Recombinant Interleukin-2.

A two-color FACS analysis with antibodies to CD4 and the indicated V β subgroups was used to determine the proportion of positive cells. The analysis was gated for lymphocytes. The upper panel shows the percentage of cells that were positive for both CD4 and the indicated V β subgroups before and after six courses of interleukin-2. Most subgroups increased roughly in proportion to the increase in the percentage of CD4 cells (19 percent before interleukin-2 therapy and 29 percent after). The lower panel indicates the relative proportion of CD4 cells accounted for by each V β subgroup. "Other" denotes V β subgroups for which antibodies were unavailable.

counts. The dose was reduced to 12 million IU per day in four patients and to 6 million IU per day in eight. One patient, who was taking trichosanthin without our knowledge, died from hypotension and lactic acidosis one week after completing the first course of interleukin-2 and two days after receiving a third dose of trichosanthin. One patient withdrew from the study after the second course of interleukin-2 and was lost to follow-up, and one patient received a single course. These three patients are not included in the analysis.

Among the six patients who could be evaluated and who had CD4 counts that were initially between 100 and 200 per cubic millimeter, two had increases of more than 50 percent in their counts (Fig. 2); both had substantial increases in cells that were positive for the interleukin-2 receptor. In contrast, none of the six patients with CD4 counts under 100 per cubic millimeter had increased CD4 counts. Furthermore, sustained increases in p24 antigen or HIV RNA levels were noted in 10 of the 12 patients. In this cohort of 12 patients, the mean (\pm SD) level of HIV RNA increased from $97,000 \pm 101,000$ to $193,000 \pm 221,000$ copies per milliliter, and the level of p24 antigen increased from 60 ± 67

to 268 ± 478 pg per milliliter. Opportunistic infections developed in two of the patients with fewer than 100 CD4 cells per cubic millimeter; they died approximately two and seven months after the last course of interleukin-2. Despite the lack of increases in the CD4 count, increases in the expression of the interleukin-2 receptor and decreases in the expression of HLA-DR were commonly seen in this group (Fig. 2), suggesting that the effect of interleukin-2 on the CD4 count in patients with HIV infection may depend on the balance between the ability of interleukin-2 to cause an expansion of CD4 cells and the ability of HIV to cause their destruction.

DISCUSSION

These preliminary observations suggest that interleukin-2 can reverse some of the serious immunologic abnormalities characteristic of HIV infection, especially the depletion of CD4 T lymphocytes. The maximal immunologic benefit with interleukin-2 therapy was seen in the patients without a severe immunodeficiency and with a low viral burden. Although the administration of antiretroviral agents alone or in combination can lead to increases in CD4 counts, such increases are transient and not of the magnitude seen in this study (Fig. 1).¹⁻⁵ After the discontinuation of interleukin-2, responses were sustained for up to eight months in some patients and could be reinduced by the administration of additional interleukin-2. The analysis of V β subgroups showed that the CD4 cell increases were polyclonal, suggesting an expansion of the available repertoire of CD4 cells. A previous study, in which polymerase-chain-reaction techniques were used to analyze V α and V β subgroups in patients with cancer receiving interleukin-2, reported a similar polyclonal increase in T-cell populations.³⁰

As compared with healthy controls, HIV-infected patients have an increased percentage of peripheral-blood lymphocytes expressing HLA-DR,^{31,32} representing an increased proportion of activated lymphocytes in the peripheral blood. This increase is seen primarily in CD8 T lymphocytes and may be a sign of a poor prognosis.³³ Interleukin-2 therapy resulted in a decline in the numbers of CD8 cells that were expressing HLA-DR. Such declines were seen in almost all patients, even in the absence of an increase in CD4 cells and regardless of the initial CD4 count. This decline may represent an interleukin-2-induced improvement in the aberrant homeostatic mechanisms that regulate the activation and differentiation of CD8 lymphocytes in patients with HIV infection.

The proportion of cells that were positive for the interleukin-2 receptor increased during therapy, primarily among the patients whose CD4 counts increased. Cells that are positive for the interleukin-2 receptor can presumably respond more readily to interleukin-2 therapy and may play a part in sustaining the increase in CD4 cells.

The precise mechanisms underlying these effects are under study. The intermittent administration of interleukin-2 may be analogous to the alternating cycles of

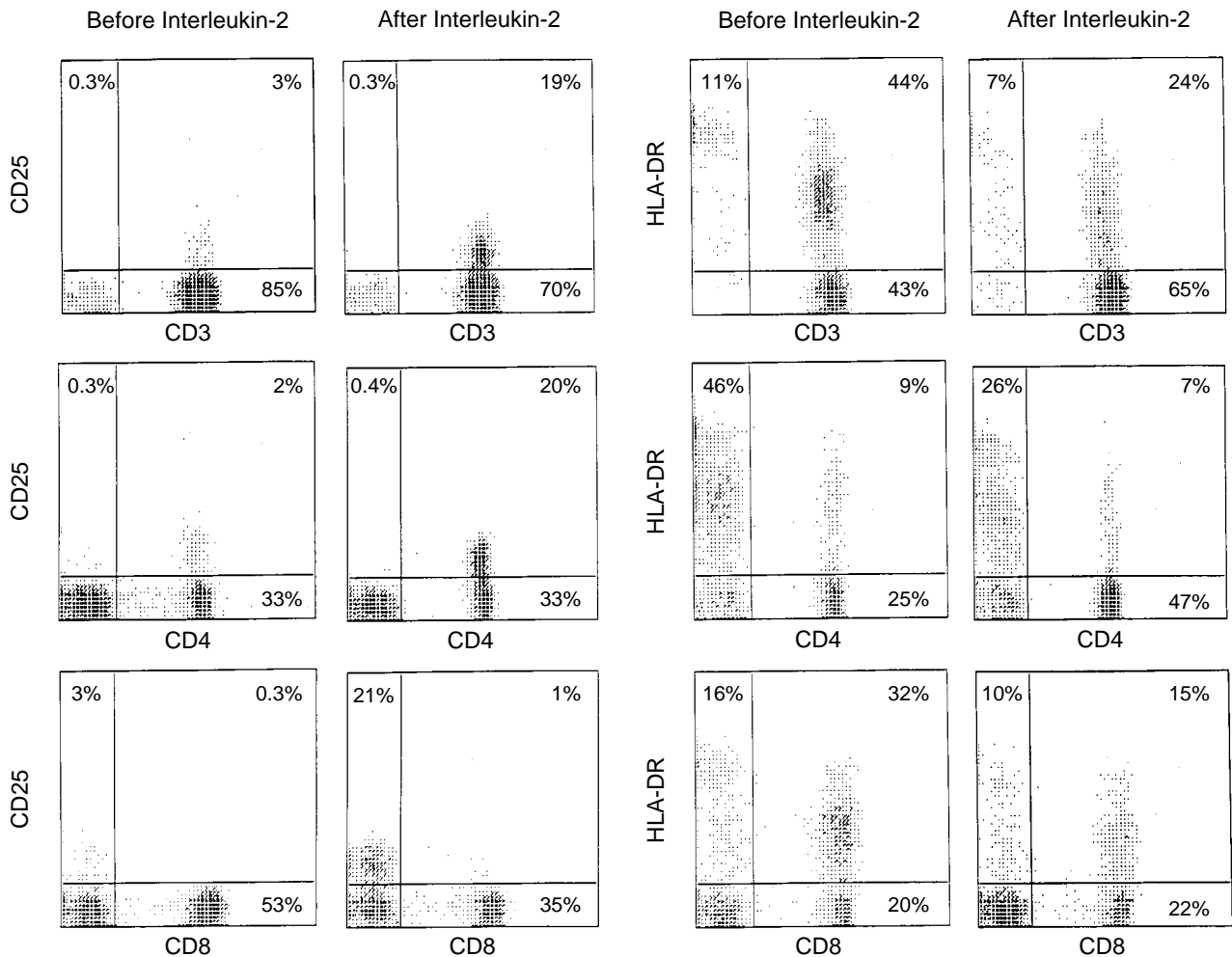


Figure 4. Two-Color FACS Analysis of the Expression of the Interleukin-2 Receptor (CD25, Left-Hand Panels) and HLA-DR (Right-Hand Panels) on Frozen Cells Obtained from Patient 2 before Interleukin-2 Therapy and at Week 48 (Five Weeks after the Fifth Course of Interleukin-2).

The increase in the interleukin-2 receptor is due primarily to its increased expression on CD4 cells, and the decline in the expression of HLA-DR is due primarily to its decreased expression on CD8 cells. The FACS analysis was gated for lymphocytes. The mean (\pm SD) normal value for cells that are positive for CD3 and the interleukin-2 receptor is 4.4 ± 1.5 percent; for cells that are positive for CD3 and HLA-DR, it is 8.7 ± 2.9 percent.

stimulation and rest needed for the expansion of T-cell lines or clones in vitro.³⁴ We believe the findings described here are due to a pharmacologic effect of interleukin-2 on the human immune system, resulting in an increase in the rate of lymphocyte production. This effect may be even more marked in patients without HIV infection, such as those with tuberculosis. In patients with HIV infection, interleukin-2 may also prolong the survival of T cells by altering programmed cell death mediated by HIV envelope proteins or by cytokines.^{35,36} In addition, exogenously administered interleukin-2 may reverse the imbalance between interleukin-2 and interferon gamma or alter the balance between T helper type 1 and T helper type 2 CD4 lymphocytes.³⁷⁻⁴⁰

On the basis of the branched-DNA assay, it appears that interleukin-2 can transiently increase the concentration of HIV particles in plasma in patients with high

CD4 counts and may lead to sustained increases in the viral burden in patients with low CD4 counts (especially in those with fewer than 100 cells per cubic millimeter). Although no obvious detrimental effects of this viral induction were noted, it seems prudent to maximize the antiretroviral regimen while administering interleukin-2, perhaps by using two or more antiretroviral drugs in combination. In Patient 3, an improvement in the suppression of viral replication, as evidenced by a decrease in particle-associated HIV RNA after the addition of didanosine, was associated with an enhanced response to interleukin-2 (Fig. 1). When this burst of viral activity is better understood, it may prove to be a useful in vivo model for the rapid clinical evaluation of potential antiretroviral agents.

Our results differ from those of other studies using low doses of recombinant interleukin-2 or its polyethylene glycol derivative administered subcutaneously. In

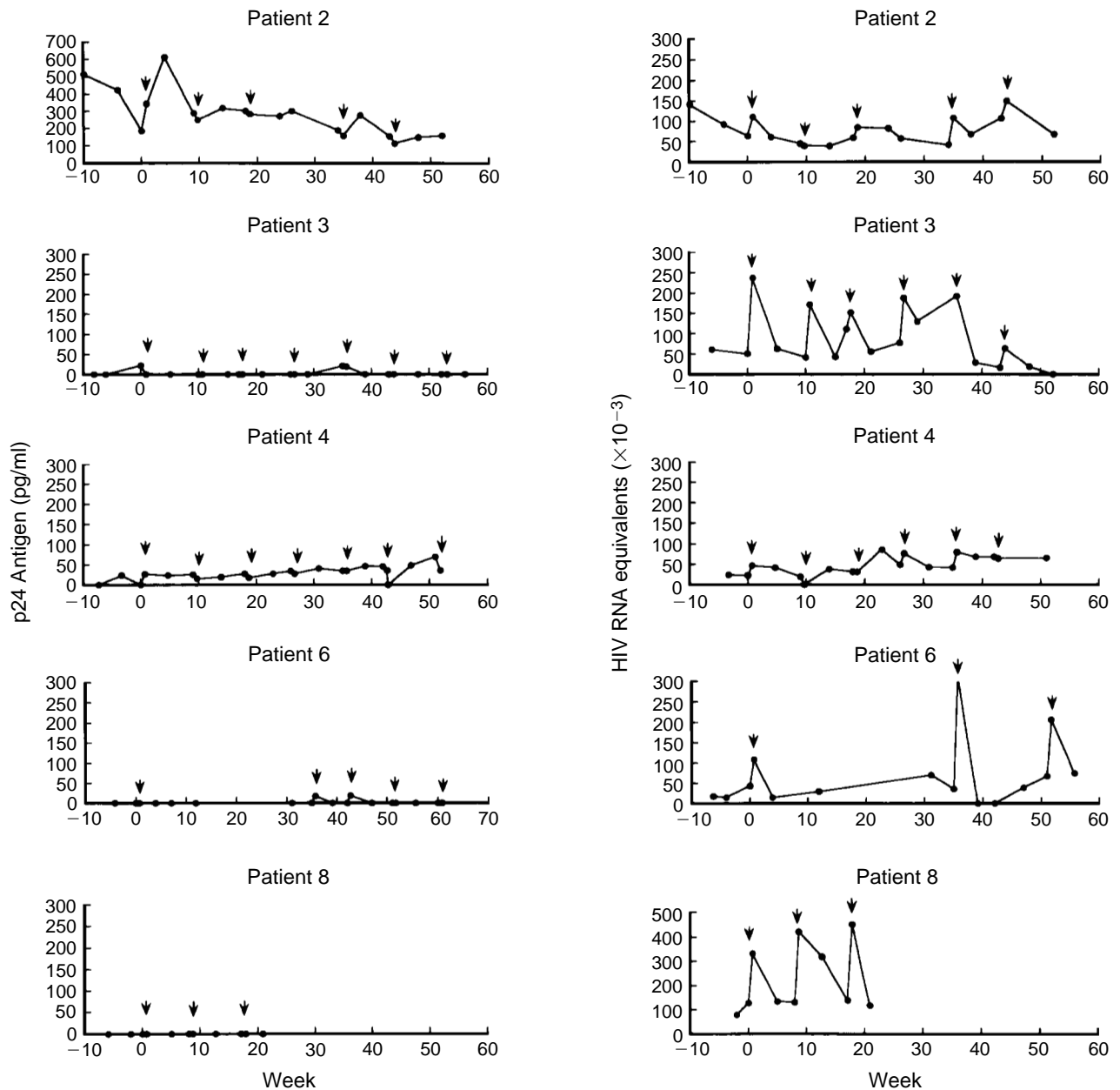


Figure 5. Changes in Viral Markers during Interleukin-2 Therapy in Five Patients with CD4 Counts Higher Than 200 per Cubic Millimeter and Detectable Levels of HIV RNA during the Study.

The results are shown for samples obtained four and eight weeks after each course of interleukin-2, as well as for those obtained five or six days after (arrows) the beginning of each five-day course of interleukin-2. There were no significant changes in p24 antigen levels during interleukin-2 therapy (left-hand panels). Particle-associated plasma HIV RNA levels (right-hand panels) tended to increase transiently immediately after interleukin-2 therapy, then returned to base-line values. All the patients were receiving zidovudine throughout the study, and Patient 3 was also receiving didanosine from week 38 onward. In four other patients, both p24 antigen and HIV RNA levels were undetectable at almost all times, and in one patient frozen samples were unavailable for the branched-DNA assay.

those studies, changes in CD4 and CD8 counts and in the expression of HLA-DR and the interleukin-2 receptor were less marked and more transient than the changes we observed.^{15,41} Intravenous administration of interleukin-2 has been reported to cause a modest increase in the CD4 count.^{11,12} Furthermore, although the activity of natural killer cells has been shown to increase with low doses of interleukin-2,^{15,42} we ob-

served no consistent changes in the activity of these cells or lymphokine-activated killer cells after interleukin-2 therapy (data not shown).

This study has also demonstrated the potential role of the branched-DNA assay in monitoring viral activity by measuring levels of particle-associated HIV RNA.²⁴⁻²⁶ Similarly, the reverse transcriptase-polymerase chain reaction, another technique for measuring

levels of HIV RNA, has recently been reported to show promise.⁴³ Many of the other current markers of the viral load, such as p24 antigen levels and plasma viremia, are less informative because of their lower sensitivity or poorer reproducibility. A direct comparison of the branched-DNA assay with the other assays, especially the reverse transcriptase-polymerase chain reaction, should help identify the optimal quantitation technique.

The clinical importance of the transient burst in viral RNA after an infusion of interleukin-2 is uncertain. Preliminary data suggest that this burst may be due to the expression of previously silent proviral DNA, possibly through the increased integration of proviral DNA or increased transcription due to the global T-cell activation induced by interleukin-2. Our four patients with the most dramatic increases in the CD4 count (Patients 1, 7, 9, and 10) all had undetectable levels of HIV RNA before and during therapy. In Patient 1 quantitative microcultures of frozen cells for HIV were also negative at all times (data not shown), suggesting that the degree of immunologic enhancement induced by interleukin-2 is inversely proportional to the viral burden.

Interleukin-2 clearly merits further evaluation as a treatment for patients with HIV infection or other diseases characterized by decreased T-cell function, including infections with fungi or mycobacteria. In patients with HIV infection, interleukin-2 may have a role in preventing the deterioration of the immune system to a level that renders patients susceptible to opportunistic infections. As with any intervention, the potential benefit of interleukin-2 will need to be carefully weighed against its potential side effects.

It is clear from our data that the use of interleukin-2 in patients with initially low CD4 counts (≤ 200 per cubic millimeter) does not result in the increased counts seen in patients with initially high CD4 counts (> 200 per cubic millimeter). Thus, if intermittent interleukin-2 therapy has a clinical benefit in patients with HIV infection, it will most likely be seen in those with CD4 counts above 200 cells per cubic millimeter. Controlled trials with clinical end points are needed for definitive evidence of such a benefit. The ongoing randomized trials should help determine the optimal use of interleukin-2 therapy and the clinical importance of these immunologic findings in patients with HIV infection.

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