Recombinant Human Gamma Interferon in Human Immunodeficiency Virus-Infected Children: Safety, CD4⁺-Lymphocyte Count, Viral Load, and Neutrophil Function (AIDS Clinical Trials Group Protocol 211)

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Received 16 October 1998/Returned for modification 30 November 1998/Accepted 22 January 1999

Nineteen children with human immunodeficiency virus (HIV) infection were treated with recombinant human gamma interferon (rIFN-γ) (50 μg/m² subcutaneously three times each week during weeks 1 through 12 and 100 μg/m² subcutaneously three times each week during weeks 13 through 24) in a phase I/II clinical trial. All children continued to receive previously prescribed therapy with oral zidovudine or didanosine. Children were assessed clinically and with laboratory studies during 24 weeks of study treatment and for 12 weeks after completion of rIFN-γ therapy. In general, rIFN-γ therapy was well tolerated. There were two clinical or laboratory adverse events thought to be possibly or probably study drug associated. One child developed acute pancreatitis; another child developed granulocytopenia. Median CD4⁺-lymphocyte counts and plasma HIV RNA concentrations did not change significantly during therapy. In vitro neutrophil bactericidal activity against Staphylococcus aureus and superoxide production were not significantly affected by rIFN-γ therapy. We conclude that rIFN-γ therapy in HIV-infected children receiving single-agent antiretroviral therapy is safe and does not produce consistent changes in CD4⁺-lymphocyte count, plasma HIV RNA concentration, or in vitro neutrophil function.

Materials and methods

Patients and study design. The study was approved by the institutional review boards of each participating institution, and institutional human experimentation guidelines were followed. Informed consent was obtained from each child's parent or legal guardian. In the case of children 7 years of age or older, assent of the minor subject also was obtained. Eligible subjects included children and adolescents, aged 1 to 17 years, with symptomatic HIV infection as defined by the U.S. Centers for Disease Control and Prevention in 1987 (3). All children had been receiving therapy with zidovudine or didanosine for more than 6 weeks at the time of study enrollment. Thirteen patients were recruited at Texas Children's Hospital, Houston, and six were recruited at Children's Hospital of Philadelphia.

All children continued to receive previously prescribed therapy with oral zidovudine or didanosine at standard doses for the duration of the study. Therapy with recombinant IFN-γ (rIFN-γ) (Genentech, Inc., South San Francisco, Calif.) (50 μg/m² subcutaneously three times each week during study weeks 1 through 12; 100 μg/m² subcutaneously three times each week during study weeks 13 through 24) was initiated on study day 1. Dose interruption and reduction

TABLE 1. Characteristics of subjects at study entry

| Characteristic   | Value              |
|-----------------|--------------------|
| No. of subjects | 19                 |
| Age             | Median 6.8 yr      |
| Range           | 14 mo to 12 yr     |
| Sex             | Male/female 7/12   |
| Race or ethnicity | African American 12|
|                 | White 2            |
|                 | Hispanic 5         |
| Antiretroviral therapy | Zidovudine 12 |
|                 | Didanosine 7       |

Human immunodeficiency virus (HIV) infection is associated with important perturbations of normal cytokine production. Decreased production of type 1 cytokines (gamma interferon [IFN-γ] and interleukin 2 [IL-2]) and increased production of type 2 cytokines (IL-4 and IL-10) among children with vertical HIV infection have been described (20). An important role for type 1 cytokines in HIV disease pathogenesis has been suggested by the finding that in vitro T-cell receptor-induced programmed CD4⁺-cell death (apoptosis) can be blocked by addition of exogenous IFN-γ and IL-2 (4). In addition, IFN-γ can reduce in vitro HIV infectivity in human monocytes (7, 8, 10). Decreased neutrophil function in HIV-infected children has been described (9, 16).

In vitro addition of IFN-γ to HIV-positive-patient-derived monocytes or mixed lymphocyte populations can correct deficient activity against Toxoplasma gondii (5) and Cryptococcus neoformans (11), two important pathogens of patients with AIDS. In vivo treatment with IFN-γ can restore the toxoplasmastatic activity of monocytes from AIDS patients (6), and case reports suggest a beneficial role for adjunctive therapy with IFN-γ in patients with AIDS and disseminated Mycobacterium avium-M. intracellular complex infection (18). Taken together, these studies suggest a possible role for IFN-γ in the prophylaxis or treatment of complicating infections in individuals with HIV infection.

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were prescribed in the protocol for a variety of potential drug-associated toxicities. All patients received prophylaxis for *Pneumocystis carinii* pneumonia, and nutritional support and antibiotic therapy were prescribed as needed. The use of immunomodulators (other than intravenous immunoglobulin) or antiretroviral agents (other than zidovudine or didanosine) was prohibited.

**Clinical and routine laboratory monitoring.** Children were evaluated clinically at baseline and every 4 weeks through study week 36. A complete blood count, absolute neutrophil count (ANC), and routine blood chemistries (aspartate aminotransferase [AST], alanine aminotransferase [ALT], blood urea nitrogen, creatinine, and total bilirubin) were monitored at baseline and every 4 weeks through study week 36. Immunologic monitoring included lymphocyte phenotyping (ACTG [AIDS Clinical Trials Group] certified laboratories at Baylor College of Medicine and Children’s Hospital of Philadelphia) at baseline and at weeks 12, 24, and 36. Virologic evaluations included the measurement of plasma HIV RNA concentrations at baseline and at weeks 12, 24, and 36. Complete HIV RNA measurements were performed at Baylor by using spin-column technology and chemiluminescence assays of PCR products (13). At Children’s Hospital of Philadelphia, nucleic-acid-sequence-based amplification was employed (Organon Teknika, Durham, N.C.).

**Assessment of phagocyte function. (i) Cell preparation.** Neutrophils were obtained from venous peripheral blood (weeks 0, 8, 20, and 32) for bactericidal activity measurements and every 4 weeks for superoxide production assays) and purified by dextran sedimentation and hypotonic lysis of erythrocytes (14). Bacterial activity and superoxide production studies were performed within 2 h of cell separation.

(ii) **Bactericidal assay.** Neutrophil killing of *Staphylococcus aureus* was assessed only for the 13 Baylor patients by a colorimetric technique modified from that used by Stevens et al. (19). Bacteria were grown overnight in a shaking incubator at 37°C, washed once with Dulbecco’s phosphate-buffered saline plus 0.2% glucose, and adjusted to a concentration of 5 × 10⁷/ml. After bacteria and cells were incubated for 1 h, 0.3% saponin (S-1252; Sigma) was added to each well. Fifty microliters of a 2-mg/ml concentration of MTT dye (M-2128; Sigma) was added to the wells. The supernatant was aspirated, and 150 μl of tissue culture medium was added to each well and incubated for 4 h at 37°C. The rate of superoxide production was determined by the superoxide dismutase-inhibitable reduction of ferricytochrome c as previously described (1). Cells were incubated with the reaction solution containing 150 μM ferricytochrome c type VI (Sigma) in Hanks balanced salt solution, pH 7.3 to 7.4, at 37°C with 100 μg of catalase and 100 ng of phorbol myristate acetate per ml with or without 100 mg of superoxide dismutase per ml. Microtiter plates were incubated at 37°C, and change in absorbance was measured at 550 nm, with absorbance at 505 nm as the reference standard. Measurements were done in triplicate at 10-min intervals up to 1 h. Results were expressed as nanomoles of superoxide produced by 10⁶ cells per 10 min.

**Statistical analysis.** The statistical significance of changes over time was tested by the Wilcoxon matched-pairs signed-ranks test. Binominal probabilities were used to test the statistical significance of the tendency for the patient values on the bactericidal assay to fall below those of the daily controls at each time point.

**RESULTS**

**Baseline patient characteristics.** Nineteen children were enrolled in the study between August 1993 and July 1995. Selected characteristics of the study population are shown in

| TABLE 3. CD4⁺-lymphocyte counts in patients receiving rIFN-γ<sup>a</sup> |
|---|---|---|---|---|
| Study wks | Change in CD4⁺ lymphocyte count (cells/μl) | P (Wilcoxon) |
| Median | Mean |
| 0–12 | −1 | −16 | 0.41 |
| 12–24 | −64 | −40 | 0.09 |
| 24–36 | −56 | −34 | 0.04 |

<sup>a</sup> Restricted to 13 patients with complete data.

| TABLE 4. Plasma HIV RNA concentrations in patients receiving rIFN-γ<sup>+</sup> |
|---|---|---|---|---|
| Study wk | Change in HIV RNA concn (log<sub>10</sub> copies/ml) | P (Wilcoxon) |
| Median | Mean |
| 0–12 | −0.09 | −0.07 | 0.32 |
| 12–24 | −0.11 | −0.03 | 0.77 |
| 0–24 | −0.22 | −0.10 | 0.63 |
| 24–36 | −0.09 | −0.09 | 1.00 |

<sup>+</sup> Only 10 patients with complete data from weeks 0, 12, and 24 were included.

**FIG. 1.** Neutrophil bactericidal activity in 13 patients treated with rIFN-γ. Values are the percentages of the neutrophil killing of *S. aureus* by controls. Subjects were given subcutaneous rIFN-γ (50 μg/m²) during weeks 1 to 12 and 100 μg/m² during weeks 13 to 24. The median values are indicated by horizontal lines in the columns.
TABLE 5. Comparison of bactericidal activity by patient and control neutrophils

| Study wk | Median control (% kill) | Median ratio (treated/control) | Median % difference (treated/control) | \( p^a \) | Median % change from baseline | \( p^b \) |
|----------|-------------------------|-------------------------------|--------------------------------------|-------|-----------------------------|-------|
| 0        | 79                      | 0.67                          | -25                                  | <0.001|                              |       |
| 8        | 76                      | 0.49                          | -37                                  | <0.001| 6.4                         | 0.35  |
| 20       | 78                      | 0.76                          | -18                                  | <0.001| 6.2                         | 0.63  |
| 32       | 71                      | 0.79                          | -14                                  | <0.004| 0                           | 0.24  |

\( a \) At each time point, patients exhibited lower values than healthy controls. The \( P \) values are binomial probabilities assessing the probability that this could have happened by chance.

\( b \) Treated subjects versus subjects at week 0. The \( P \) values were calculated with Wilcoxon matched-pairs tests assessing the statistical significances of a change from the baseline.

Table 1. All of the children had vertically acquired HIV infection.

Safety. Therapy with rIFN-\( \gamma \) was well tolerated by most children (Table 2). Four children developed a fever between 38.5 and 40.0°C which lasted for less than 48 h after one or more rIFN-\( \gamma \) injections. Moderately severe vomiting and anorexia were observed in a 6-year-old girl who developed pancreatitis of unknown etiology. One patient developed mild vomiting and one developed anorexia during the course of the study. Two children developed liquid diarrhea; one case was associated with mild dehydration.

Adverse events observed in laboratory evaluations during the course of the study included moderate or more severe (toxicity grade 2 or higher) abnormalities of ANC, blood hemoglobin concentration, platelet concentration, serum bilirubin concentration, serum ALT concentration, and serum AST concentration (Table 2).

There was no apparent relationship between rIFN-\( \gamma \) dosage or duration of drug exposure and occurrence of clinical or laboratory adverse events. Only two clinical or laboratory adverse events were assessed by the investigators as possibly or probably study drug associated. A 6-year-old girl developed pancreatitis of unknown etiology at study week 4. Therapy with both didanosine and rIFN-\( \gamma \) was permanently discontinued, and the pancreatitis resolved after a severe illness and a prolonged course of hospitalization. An 18-month-old boy with a baseline ANC of 1,300/\( \mu \)l developed ANC values as low as 380/\( \mu \)l while receiving zidovudine and rIFN-\( \gamma \). Treatment with rIFN-\( \gamma \) (but not zidovudine) was interrupted temporarily at study weeks 6 and 20 and discontinued permanently at study week 24 without an obvious effect on subsequent ANC values. Two other children discontinued study treatment prematurely due to HIV disease progression and parental request.

Clinical observations. Compared with age-appropriate normal values (17), the median 6-month weight-growth velocity for the 15 children evaluable after receiving rIFN-\( \gamma \) for 24 weeks reached the 15th percentile. Seven children had 24-week weight-growth velocities below the 10th percentile for their age.

No AIDS-defining symptoms were observed during the course of study treatment. A 2-year-old girl developed Streptococcus pneumoniae bacteremia during study week 16 and pulmonary tuberculosis during study week 24. A 20-month-old girl developed what was thought to be HIV-associated pancytopenia during study week 12 and died shortly thereafter of hemorrhagic brain infarction.

Immunologic and virologic observations. Exploratory longitudinal analyses of CD4\( ^+ \)-lymphocyte counts and plasma HIV RNA concentrations did not reveal consistent changes (Tables 3 and 4). The median baseline absolute CD4\( ^+ \)-lymphocyte count for the 13 children with complete data for the 36 weeks of study was 331/\( \mu \)l (range, 0 to 1,047/\( \mu \)l). The same children had median absolute CD4\( ^+ \)-lymphocyte counts of 298, 191, and 232/\( \mu \)l at study weeks 12, 24, and 36, respectively. Analysis of change in CD4\( ^+ \)-lymphocyte count was restricted to patients with complete data from study weeks 0, 12, 24, and 36. Table 3 indicates that there was no essential change between weeks 0 and 12, there was a nonsignificant decline between weeks 12 and 24, and there was an apparent gain during the follow-up period between weeks 24 and 36. A Wilcoxon sum ranks test indicated that the gain after discontinuation of rIFN-\( \gamma \) therapy was statistically significant, but given the overall pattern of changes, this increase may represent a chance occurrence. CD8\( ^+ \)-T-cell counts and T-cell subset percentages did not differ.

The median baseline plasma HIV RNA concentration among the 10 children at Baylor with complete data for the 36 weeks of study was 14,470 copies/ml (range, 1,512 to 496,800). The same children had median plasma HIV RNA concentrations of 12,850, 14,580, and 10,040 copies/ml at study weeks 12, 24, and 36, respectively. Analysis of change in plasma HIV RNA concentration was restricted to a subgroup of 10 patients from Baylor whose results came from the same assay and who had complete data from study weeks 0, 12, and 24. Table 4 shows that these patients had modest decreases in plasma HIV RNA concentration, with a median decline of 0.22 log\( _{10} \) copies/ml from baseline to the end of treatment at week 24. A Wilcoxon matched-pairs test indicated that the observed changes were not significant. Plasma HIV RNA concentrations also were measured in the eight subjects at Children’s Hospital of Philadelphia, but because the values were obtained with a different RNA assay, only the Baylor data are shown. The RNA values obtained on these eight subjects did not show significant change with rIFN-\( \gamma \) therapy.

Neutrophil function. No significant change was observed during the course of the study in neutrophil bactericidal activity against S. aureus relative to week 0 (Table 5; Fig. 1). Because of the decrease in the median value at week 8, there appears to be an increase in bactericidal activity at weeks 20 and 32. It is possible that a study with additional subjects would clarify whether this apparent increase is real. Variability between controls was considerably lower, with almost all controls recording 70 to 95% killing (data not shown). At weeks 20 and 32 only, one patient had a value of killing that was less than 50% of the control value, as contrasted to several patient values less than 50% of the control value at weeks 0 and 8. Patient values were significantly less than control values at all time points (Table 5).

Patients were assessed every 4 weeks for non-receptor-mediated (i.e., phorbol myristate acetate-induced) superoxide production. Values ranged from 0.6 to 58.9 nmol/10\(^6\) neutro-
phils/10 min. IFN-γ failed to produce significant changes in values (Table 6) over the course of the study.

DISCUSSION

There is theoretical support for use of immune modulators, including rIFN-γ, for restoration or correction of HIV-induced immune dysfunction. A previous phase I/II trial of rIFN-γ (10 μg/m² intramuscularly three times each week for 16 weeks) in adults with AIDS-related complex did not lead to either beneficial or detrimental changes in immunologic or virologic markers of HIV disease status (2). The present study was conducted to derive preliminary information on the tolerance, safety, and immunologic and virologic effects of rIFN-γ in HIV-infected children receiving long-term zidovudine or didanosine therapy.

Therapy with rIFN-γ generally was well tolerated in this population of children with symptomatic HIV infection. However, we found that the necessity of injections was a disincentive to enrollment and led to premature discontinuation of study treatment in three cases. Only two clinical or laboratory adverse events were judged to be possibly or probably associated with rIFN-γ treatment, but it is also possible that these events were attributable to underlying HIV disease or treatment with other medications. For example, there is a well-recognized association between didanosine therapy and the occurrence of acute pancreatitis (15), which might have accounted for one of these events.

This study was not designed to assess the clinical efficacy of rIFN-γ therapy, and all clinical findings must be interpreted in the context of advanced HIV disease. One child developed two serious bacterial infections during the course of study treatment, and a surprisingly large number of children experienced growth failure. Among HIV-infected children, 6-month weight-growth velocities below that of the 10th percentile for age and gender are associated with higher rates of mortality (12). Since rIFN-γ therapy was added to an antiretroviral therapeutic regimen (monotherapy with zidovudine or stavudine) which we now know to be suboptimal in controlling HIV-1 viral burden, it is difficult to ascribe this growth failure to rIFN-γ, since inadequate primary treatment of HIV-1 is known to be associated with growth failure.

Examination of median absolute CD4⁺-lymphocyte counts revealed a decline over the 24 weeks of study treatment that was not statistically significant, with a modest rebound in count after discontinuation of rIFN-γ therapy. Significant changes in median plasma HIV RNA concentrations were not observed, and the mechanism for any possible effect of rIFN-γ on CD4⁺-lymphocyte counts is unclear. Phagocyte function was evaluated by assessment of the bactericidal activity of HIV-infected-patient neutrophils and by their ability to produce superoxide. Neither neutrophil function was altered by giving study subjects three-times-weekly subcutaneous injections of rIFN-γ. Whether the shift in some patients’ bactericidal activity to more than 50% of control killing at 20 weeks of rIFN-γ therapy and at 8 weeks after stopping therapy has any in vivo significance is unknown.

In summary, this phase I/II trial of rIFN-γ in symptomatic HIV-infected children has demonstrated that the cytokine is safe and well-tolerated. Whether the modest changes in CD4⁺-lymphocyte counts which were observed during the trial are related to the study drug is unknown. Neutrophil bactericidal activity and superoxide production were not changed by therapy.

ACKNOWLEDGMENTS

We gratefully acknowledge R. Nelson Bennett, Pamela Bouquin, Donald Campbell, Peter Chvany, John G. Curi, Yih J. Danels, Courtney V. Fletcher, Richard Gelber, Elizabeth Hawkins, Linda M. Page, Deborah H. Schieble, Cara Singel, and Dennis Weller for technical and scientific assistance. Genentech, Inc., supplied recombinant human interferon-gamma.

This work was supported by Pediatric AIDS Clinical Trials Group grants U01-AI27551 and U01-AI35921 from the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases, NIH grants MO1-R00188 and MO1-R00240 from the General Clinical Research Centers program, NIH grant P30-AI 36211 from the Center for AIDS Research program, and grant 50425-15-PG from the Pediatric AIDS Foundation.

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### Table 6. Superoxide production by patient neutrophils

| Study wk | n  | % Median change[^a] | P    |
|----------|----|---------------------|------|
| 0–12     | 17 | +2.6                | 0.85 |
| 0–24     | 15 | +0.6                | 0.72 |
| 12–24    | 15 | +1.9                | 0.60 |
| 24–36    | 13 | 1.2                 | 0.95 |

[^a]: The median values for patients were 18.3 at week 0, 19.2 at week 12, 20.4 at week 24, and 20.2 at week 36.
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