MAJOR ARTICLE

Long-Term Interferon-γ Therapy for Patients with Chronic Granulomatous Disease

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Background. Chronic granulomatous disease (CGD) is a rare disorder of phagocytes in which absent production of superoxide and hydrogen peroxide in phagocytes predisposes patients to bacterial and fungal infections. Infections are dramatically reduced by prophylaxis with antibiotics, antifungals, and interferon-γ (IFN-γ).

Methods. Seventy-six patients with CGD were enrolled in an uncontrolled, open-label follow-up study to assess the long-term clinical safety and efficacy of IFN-γ therapy. Patients received IFN-γ subcutaneously 3 times per week.

Results. We observed patients for up to 9 years, for a total observation period of 328.4 patient-years. The incidence of serious infections was 0.30 infections per patient-year; for serious bacterial infections, the incidence was 0.18 cases per patient-year, and for serious fungal infections, it was 0.12 cases per patient-year. Thirty-seven percent of patients reported an adverse event, the most common of which was fever. Twenty-six patients withdrew from the study (3 because of adverse events, 15 because of patient preference, and 8 because of transfer to another trial). There were no life-threatening IFN-γ–related adverse events and no discernible effects on growth. The overall mortality rate was 1.5% per patient-year.

Conclusion. IFN-γ prophylaxis for CGD appears to be effective and well tolerated over a prolonged period of time.

Chronic granulomatous disease (CGD) is an inherited disorder of leukocyte function caused by defects in the reduced nicotinamide adenine dinucleotide phosphate oxidase, the enzyme complex responsible for phagocyte superoxide generation. Mutations in 4 genes cause CGD. The mutations in CYBB ($gp91^{phox}$; Xp21.1) account for two-thirds of cases; the remainder are autosomal recessive. Recurrent life-threatening bacterial and fungal infections, as well as abnormally exuberant inflammatory responses, are common [1, 2]. Granulomatous complications usually affect the gastrointestinal and genitourinary tracts, but cultures are usually sterile, and steroid therapy is usually successful [1, 3, 4].

Long-term oral trimethoprim-sulfamethoxazole prophylaxis has markedly reduced the rate of infection among patients with CGD [5–9]. Further reduction of the infection rate among persons with CGD has been achieved with IFN-γ, a proinflammatory cytokine [10]. When injected subcutaneously 3 times weekly, IFN-γ has reduced the rate of serious infection in persons with CGD by 67%. This therapy was effective for all genetic types of CGD, and children aged <10 years appeared to benefit the most. Side effects were moderate [10]. Similar results were obtained in a trial of IFN-γ in mice with CGD [11]. Despite several decades of work on IFN-γ and its many effects on phagocytes, we still do not know which mechanism(s) is/are important in infection prevention in CGD [12–17]. However, we do know that IFN-γ does not reverse the defect in superoxide production in CGD [10, 11]. After the prospective human trial was completed [10], this phase IV study of long-term efficacy and toxicity of IFN-γ was initiated.

PATIENTS, MATERIALS, AND METHODS

Study design. This study was designed to monitor the safety and efficacy of long term IFN-γ treatment

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in patients with CGD. Enrollment in this open-label study (91-I-0186) started in May 1992 and ended in July 2001. Eighty patients were enrolled. Four patients elected not to receive IFN-γ before initiation and were excluded from further evaluation. Therefore, this report is based on findings for 76 patients with CGD who received IFN-γ, all of whom or their parents gave informed consent.

CGD was confirmed by both abnormal neutrophil nitroblue tetrazolium reduction and neutrophil superoxide anion production ≤20% of normal after phorbol myristate acetate stimulation. At entry, patients had to have stopped receiving parenteral antibiotic therapy for infection ≥2 weeks earlier. Although all patients were observed at the National Institutes of Health (NIH; Bethesda, MD), some of the infectious events, side effects, or other manifestations of their underlying CGD required hospitalization or specific treatment at their home institutions. Nevertheless, every effort was made to capture and verify relevant data. Twenty-four of 76 patients were also enrolled in the previously published phase III study of IFN-γ [10]. Events from the previous prospective randomized study are not included here. This study represents only the open-label long-term use of IFN-γ in CGD.

For patients with a body surface area of ≥0.5 m^2, the dose was 0.05 mg/m^2; for those with a body surface area of ≤0.5 m^2, the dose was 0.0015 mg/kg; for both regimens, the drug was administered subcutaneously 3 times weekly. IFN-γ therapy was stopped for patients who became or were trying to become pregnant and for those who were lactating. A treatment interruption was identified if use of the drug was restarted within 2 months; a discontinuation was identified if use of the drug was stopped for longer periods.

Patients received concomitant prophylactic antibiotic therapy based on age and medication allergy. Seventy-two patients received trimethoprim-sulfamethoxazole (usually 5 mg/kg b.i.d.), 2 received only trimethoprim because of sulfa allergy, and 2 received cephalosporins. Twenty-seven patients were coenrolled in a double-blind, placebo-controlled crossover study of itraconazole prophylaxis for the prevention of fungal infections in persons with CGD [18]. Characteristics of patients are shown in table 1.

A serious infection was defined as an infection that required hospitalization or treatment with parenteral antibiotics or antifungals; these were recorded at each visit, with date, diagnosis, etiology, medications, and/or surgical procedures noted. Infections not treated at the NIH were documented and recorded. For statistical analysis, the etiology of infections without confirmed cultures was inferred if successful treatment and resolution followed use of a specific regimen (e.g., antibacterials only). Data on serious infections were analyzed for each of 4 age groups: ≤4 years, 5–12 years, 13–18 years, and >18 years. The associations between infections and CGD genotype and bacterial or fungal infections were calculated.

Adverse events were recorded with the date of onset, relationship to therapy, effect on therapy, and clinical outcome. Adverse events probably related to IFN-γ treatment were defined as "mild," if there was no change in performance; "moderate," if there was some medication required for relief; and "severe," if discontinuation or temporary interruption of IFN-γ was necessary. An inflammatory event was determined by a compatible presentation, typically inflammatory bowel disease or genitourinary obstruction, for which steroid treatment led to improvement. Gastrointestinal involvement was defined as clinical manifestations in the alimentary tract confirmed by endoscopy with granulomata and confirmed by pathological examination. The clinical manifestations of gastrointestinal involvement were persistent diarrhea without an infectious etiology (with or without blood in the stool), constipation, persistent abdominal pain unrelated to other causes, obstruction, or fistulae. Genitourinary granulomatous involvement was determined if urological manifestations were caused by granulomata in the urinary tract without infection. For persons who died during the study, the cause of death was determined by autopsy.

Clinical and laboratory evaluation. The study was designed for semiannual NIH evaluation. For those patients seen more than twice per year because of illness, only those data obtained while the patient was in good condition were entered into the database. Each entry was supposed to include medical history, physical examination findings (including weight and height percentiles), medication and treatment received, complete blood cell count, chemistry profile (albumin, creatinine, electrolytes, alkaline phosphate, and liver enzyme levels), endocrine profile (T_4, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, testosterone, and estradiol levels), and developmental evaluation by Tanner staging. All laboratory testing was done using standard assays.

Table 1. Demographic characteristics of 76 patients with chronic granulomatous disease.

Characteristic	Value
Age at diagnosis, mean (range)	5.4 years (birth to 27 years)
No. of families affected	63
Age at initiation of IFN-γ therapy, years	
Mean ± SD	14 ± 9.2
Range	1.3–27
No. (%) of male patients	61 (80)
No. (%) of patients with X-linked inheritance	50 (66)
Autosomal recessive, no. (%) of patients	
All	26 (34)
$p47^{phox}$	23
$p22^{phox}$	2
$p67^{phox}$	1

Table 2. Serious infections in patients with chronic granulomatous disease, by etiology and organ affected.

Site or type of infection	No. of infections					
	Total	Bacterial	Fungal	Viral	Mixed	No organism identified [a]
Pneumonia	69	18	33	1	2	15
Soft-tissue abscess	16	5	3	…	…	8
Lymphadenopathy	2	1	1	…	…	…
Hepatic abscess	5	5	…	…	…	…
Perirectal abscess	3	3	…	…	…	…
Clostridium difficile infection	3	2	…	…	…	1[b]

NOTE. There was >1 serious infection per patient.

[a] Culture results were negative or cultures were not done.

[b] One episode of infection responded to *C. difficile*–specific therapy, although the results of diagnostic tests were negative.

Statistical analysis. Data were extracted from the medical record charts of each patient onto Excel spreadsheets (Microsoft). Measurements of height and weight were compared with standardized national percentiles for the United States (http://www.cdc.gov/growthchart). Toxicity events were calculated by combined or stratified analyses, with paired and unpaired tests, and the analyses corresponding Z values. Survival curves were plotted using the Kaplan-Meier method and compared using the Mantel-Cox log rank test. The tests used to compare patterns of inheritance and types of infections were exact tests for testing homogeneity of Poisson parameters and were performed using the StatXact statistics package, version 5 (Cytel Software). *P* values are 2-sided. To assess whether the rates of serious infections differed in the 4 age groups, we did a permutation test, to take into account the fact that a substantial number of patients contributed months at risk and serious infection events to >1 time period, depriving the data in the different age groups of statistical independence. To compute a *P* value for this test, we did a Monte Carlo simulation with 10,000 replications, which ensured that the reported *P* value was within $\pm 1\%$ (with 95% confidence) of the true *P* value, which could not be exactly computed because of the enormous number of permutations.

RESULTS

Demographic and Clinical Data

The overall cumulative exposure to IFN-γ treatment was 328.4 patient-years. The mean duration of therapy was 4.3 years (range, 2–110 months). Only 1 patient received IFN-γ for <1 year. At study conclusion, 45 patients (59%) continued to receive IFN-γ prophylaxis; 3 patients had withdrawn from the study because of adverse advents, 8 patients discontinued IFN-γ to participate in other protocols (5 for bone marrow transplantation and 3 for gene therapy), and 15 patients discontinued IFN-γ therapy for diverse reasons, including loss of health insurance and nonadherence to treatment. Five patients died during the study.

Overall, there were 98 serious infections during the study, for a rate of 0.30 serious infections per patient-year. There were 0.10 proven bacterial serious infections per patient-year (when including those for which no organism was identified but for which the presumption was bacterial, the rate was 0.18 cases per patient-year), and there were 0.12 serious fungal infections per patient-year. The lung was involved in 70% of episodes. The etiologies of pulmonary infection were proven to be bac-

Table 3. Comparison of infections in patients with chronic granulomatous disease, by genotype.

Variable	Genotype			
	X-linked ($n = 50$)	p22^{phox} ($n = 2$)	p47^{phox} ($n = 23$)	p67^{phox} ($n = 1$)
No. of patient-years of observation	238.9	3	86.5	1
No. of serious infections per patient-year	0.26	2.33	0.33	1
No. of serious bacterial infections per patient-year	0.15	…	0.24	…
No. of serious fungal infections per patient-year	0.11	…	0.17	…
Percentage of patients experiencing ⩾1 serious infection	72	50	62	…
Percentage of patients with >1 serious infection	30	50	27	…
Percentage of patients experiencing no serious infection	28	50	38	…

Table 4. Comparison of infections in patients with chronic granulomatous disease, by age at commencement of IFN-γ therapy.

Variable	All patients (n = 76)	Age, years ≤4 (n = 11)	5–12 (n = 40)	13–18 (n = 28)	>18 (n =3 4)
No. of patient-years of observation	328.4	14.1	142.1	74.4	97.8
Percentage of patients experiencing ⩾1 serious infection	68	36	65	43	44
Percentage of patients with >1 serious infection	29	9	33	11	12
Percentage of patients experiencing no serious infection	32	64	35	57	56
No. of serious infections per patient-year	0.30	0.35	0.36	0.20	0.29
No. of serious bacterial infections per patient-year	0.18	0.28	0.20	0.09	0.20
No. of serious fungal infections per patient-year	0.12	0.07	0.16	0.11	0.08

terial in 26% of cases, were likely to have been bacterial in 22%, were fungal in 48%, and were mixed fungal and bacterial in 3%. One patient had pneumonia due to respiratory syncytial virus (table 2) [19].

There was a slightly higher rate of infections among the autosomal recessive patients (table 3). However, 2 $p22^{phox}$-deficient patients in the autosomal recessive group accounted for 7% of infections on their own. The rates of serious infection among the stratified age groups were basically the same ($P = .44$) (table 4).

Twenty-seven nonserious infections included impetigo, folliculitis, and dermatophytoses (29% of infections); infectious sinusitis (33% of infections); and nonsuppurative lymphadenitis, otitis, pharyngitis, and blepharoconjunctivitis constituted the remainder.

Safety

Adverse events. Forty-seven patients (62%) reported no adverse events, and the majority (73%) of the reported events were mild or moderate. The expected and observed IFN-γ–related adverse events included fever, headaches, myalgias, fatigue, irritability, and flulike syndrome. No life-threatening events could be directly attributed to the administration of IFN-γ. Fever was the most frequent adverse event; concomitant administration of acetaminophen appeared to be effective. Seventeen percent of the patients had severe adverse events. Three patients (4%) withdrew from the protocol (1 because of recurrent exacerbations of ureteral granulomata and 2 because of myalgias). In 10 patients (13%), administration of IFN-γ was interrupted as a result of adverse events (i.e., fever, fatigue, and/or irritability) and reinitiated following improvement of symptoms. The adverse events leading to discontinuation of IFN-γ therapy occurred in the oldest population. However, comparison of the incidence of overall adverse events by age showed only borderline statistical difference for myalgia in patients >12 years of age (table 5).

Neutropenia, eosinophilia, and abnormal liver function test results have been described in association with the use of IFN-γ [20, 21]. Although they were seen in the current study as well, the association with IFN-γ therapy was not definite, because the patients were receiving other drugs (e.g., trimethoprim) or had concomitant infections. There were no interruptions of IFN-γ therapy resulting from abnormal laboratory findings. For each abnormal laboratory finding during the study, a more likely clinical cause was identified, and such findings resolved once the suspected offending agent or process was removed.

Renal failure developed in 2 patients and was probably related to prior amphotericin use. Reactive airways developed in 2 patients; these were thought to be due to recurrent lung infections and scarring. No malignancy was identified.

Although the prospective prophylactic study suggested a benefit in terms of prevention of granulomatous lesions in IFN-γ recipients [10], there were too few cases to make statistical comparisons. In addition, concern remained regarding the use of a proinflammatory cytokine in patients at risk for inflam-

Table 5. Adverse reactions associated with the use of IFN-γ, by age of recipients.

Event	No. of events, by patient age ≤12 years[a]	>12 years[b]	P
Fever	11	9	NS
Fatigue	1	5	NS
Myalgia	0	7	.048
Rash	4	1	NS
Headache	2	3	NS
Abdominal pain	0	2	NS
Granulomatous colitis	1	1	NS
Irritability	1	0	NS
Flulike syndrome	0	1	NS

NOTE. More than 1 event per patient was possible. P values reflect a combined or stratified analysis.

[a] Cases comprise a total of 1797 months at risk; adverse events occurred in 12 patients.

[b] Cases comprise a total of 2143 months at risk; adverse events occurred in 17 patients.

Table 6. Causes of death in IFN-γ recipients.

Patient	Age at death, years	Duration of IFN-γ therapy, years	Genotype	Cause of death
1	5	2.2	gp91^{phox}	Bacterial and fungal pneumonia
2	5	2.1	gp91^{phox}	Intra-abdominal catastrophe
3	21	5.4	gp91^{phox}	*Aspergillus nidulans* pneumonia
4	30	1	p67^{phox}	Chronic *Aspergillus terreus* pneumonia
5	17	1	gp91^{phox}	Mixed fungal pneumonia

matory lesions. Symptomatic gastrointestinal involvement was recorded in 23 patients (30%) during the course of the protocol; 12 of the 23 patients had gastrointestinal manifestations before receiving IFN-γ therapy, 10 developed gastrointestinal manifestations after initiation of IFN-γ, and 1 had gastrointestinal involvement diagnosed concomitant with the commencement of IFN-γ therapy. The prevalence of symptomatic gastrointestinal involvement in IFN-γ recipients was similar to the rate seen in patients with CGD observed at the NIH who did not receive IFN-γ over the same period (data not shown) [21]. Symptomatic genitourinary inflammatory involvement was reported in 6 patients (8%).

Growth and development. No adverse effects on growth or development were directly associated with the use of IFN-γ. At study entry, 52 patients (68%) were ⩽18 years of age. The majority of patients maintained steady growth and development during the study. Eight children (15%) were below the fifth percentile in height at least once during the study, 2 (4%) were below the fifth percentile for weight, and 6 (12%) were below the fifth percentile for both weight and height. At study termination, 3 of 33 patients aged >18 years had adult stature below the fifth percentile. Patients consistently tracked along their own growth curves, including low ones, except for periods around the time of acute infections. All of these adults had tracked along these same curves previously. We could not adjust for confounding factors, such as concomitant receipt of treatment (steroids) or parental height.

The safety of IFN-γ during pregnancy and lactation has not been established. Therefore, women trying to become pregnant or becoming pregnant during the course of this study discontinued IFN-γ therapy. During this study, 4 women became pregnant. Three patients restarted IFN-γ therapy after delivery and weaning of healthy babies; 1 had an elective abortion. Three men fathered healthy children while receiving IFN-γ prophylaxis.

Deaths. Five patients (6.6%), all X-linked, died during the protocol, at a median age of 17 years (table 6), for a mortality rate of 1.52 deaths per 100 patient-years of observation. Three deaths were due to fungal infection, and 2 were due to predominantly bacterial causes.

DISCUSSION

Careful attention must be paid to any drug that will be given to children and throughout life. Only 1 other cytokine, G-CSF, has been used for any considerable period [22]. Separating the effect of that cytokine from the complications of the underlying disease (e.g., leukemia) has proven to be difficult. In the case of CGD, the natural history of the disease is fairly well known and documented, allowing a clearer examination of the effect of long-term cytokine therapy [10, 23].

IFN-γ was well tolerated in patients with CGD. Fever was common, but treatment with acetaminophen was effective. Although 38% of patients had a drug-related adverse event, most of them restarted therapy. Given the high rate of successful reinitiation of therapy and the overall long-term tolerability, these transient intolerances may have been due to inapparent or subclinical infections. Only 3 patients (4%) had to withdraw from the study for reasons related to IFN-γ therapy. No patient experienced a life-threatening adverse event related to IFN-γ therapy.

Inflammatory manifestations, especially granulomatous involvement of the gut, have been recognized as central to CGD [24–26]. Therefore, there has been trepidation about the use of this prototypical Th1 cytokine in patients at risk for granulomatous complications. We identified gastrointestinal complications in 30% of patients. However, there was no statistical difference between the frequency of inflammatory bowel disease in patients with CGD receiving IFN-γ and NIH-observed patients with CGD not receiving IFN-γ [21]. There was no increase in granulomatous complications in IFN-γ recipients in the previous randomized trial [10]. Overall, clinically apparent granulomatous inflammation of lymph nodes, liver, and lung occurred in fewer of our patients receiving IFN-γ than in a recent European report without IFN-γ [27]. Therefore, we believe that IFN-γ is not a significant cause of inflammatory complications in CGD. Although IFN-γ may reduce the number of extraintestinal granulomatous complications by reducing the number of infections in patients with CGD, overall, it appears to be neutral in the development of inflammatory bowel disease, at least in those with CGD [21].

Table 7. Summary of the published and current studies on the use of IFN-γ in patients with chronic granulomatous disease.

Characteristic	Study (year)								
	[10] (1990)	[10] (1991)	[30] (1995)	[31] (1995)	[26] (1999)	[32] (2000)	[27] (2000)	[37] (2000)	Present study
Method	Double-blind, randomized, phase III, prospective	Double-blind, randomized, phase III, prospective	Phase IV, prospective	Phase IV, prospective	Questionnaire survey, retrospective	Retrospective	Retrospective	Questionnaire survey, retrospective	Phase IV, prospective
No. of patients	65	63	30	28	221[a]	21	39	368[a]	76
Duration of follow-up, years	0.9	…	1	3	39[b]	10	22	NR	9
Duration of therapy, patient-years	95	…	31	68.4	NR	70	610[a]	NR	328.4
Serious infection rate, cases/ patient-years	1.1	0.3	0.13	0.4	NR	0.11	0.27[c]	NR	0.3
Mortality rate, %	0	…	0	0	23.1	0	20	17.5	6.6
Subjects treated with IFN-γ, %	0	100	100	100	12	0	NS	73	100

NOTE. NR, not reported; NS, not specified.

[a] Includes living and deceased patients.

[b] Retrospective records, calculated on the basis from date of birth.

[c] A rate of 0.79 overall infections per patient per year.

Variations in height and weight are likely to be affected by chronic infections, gastrointestinal granulomatous involvement, and prolonged corticosteroid therapy. Children with CGD tend to be shorter than their peers and grow later into life than do healthy children, but the final stature of patients with CGD has been thought to be normal [28]. We found no evidence of delay in endocrinologic development (data not shown). There have been multiple minor effects of IFN-γ noted on endocrine (ACTH and cortisol) and inflammatory (IL-6 and IL-8) pathways [29]. However, our data show that prolonged IFN-γ therapy permits normal growth and development.

We reviewed the literature for studies reporting incidences of infection and mortality in patients with CGD, with special attention to the use of IFN-γ. We attempted to express the infection and mortality rates in patient-years of exposure, as well as the era in which the study was done, to take into account the changes in therapy of CGD in general, especially when the use of antifungals was concerned. We compared our rate of 0.30 serious infections per patient-year with the rates of serious infections with other phase IV studies, when we could determine or infer them. The first prospective study of infections in persons with CGD [10] was large and randomized (128 patients), but the duration of follow-up was short (~10 months). Because subjects were randomized to receive IFN-γ or placebo, it offered a baseline against which other studies may be compared. In the placebo arm of that study, the infection rate was 1.1 cases per patient-year, whereas the infection rate in the IFN-γ arm was 0.38 cases per patient-year. Weening et al. [30] found an infection rate of 0.13 cases per patient-year, whereas Bemiller et al. [31] found 0.4 serious infections per patient-year in a North American study. Cale et al. [32] reported an incidence of 0.11 infections per patient-year in an English cohort with CGD treated with prophylactic antibiotics and itraconazole without IFN-γ. Differences in the infection rates between the different studies may reflect durations and intensities of observation (table 7). The discrepancies in these various reports may also reflect differences in cohort composition, environmental exposure, or compliance [32–35]. In the current study, we had a substantially longer period of observation and significantly more patients under direct surveillance than previous studies have had.

Mortality rates have varied widely in patients with CGD. The Study Group of Phagocyte Disorder of Japan reported an overall mortality rate of ~23% in their retrospective study [36]. Of interest, only 15 of 122 patients received IFN-γ in their study [36]. In 2000, Liese et al. reported data on 39 European patients, with a calculated experience of 610 patient-years, and found an overall mortality rate of 20% [27]. Winkelstein et al. [37] found an overall mortality rate of 17.5% in their retrospective report, but the mortality was only 8.8% over the 5 years of study for those alive at entry. Therefore, our mortality rate of 6.6% over 9 years or 1.5% per patient-year appears to be a significant improvement.

The natural course of CGD has changed dramatically with the development of prophylactic trimethoprim-sulfamethoxazole, itraconazole, and IFN-γ [18, 38–41]. The prolonged use of IFN-γ in patients with CGD appears to be safe and shows persistent reduction in the frequency of serious infection and mortality. We did not see serious toxicities with long-term use. The precise mechanism whereby IFN-γ improves host defense in patients with CGD remains unclear, because it does not reverse the underlying defect in CGD, as was originally envisioned. However, the decreased rate of infections, the improved infection-free survival, and the lack of significant toxicity suggest that the initial enthusiasm for IFN-γ therapy for CGD was—and continues to be—well founded.

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Conflict of interest. All authors: No conflict.

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