REPORT

Recombinant gamma interferon for the treatment of pulmonary and mycobacterial diseases

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ABSTRACT

An increased antibiotic resistance is described for *Mycobacterium tuberculosis* and atypical mycobacterial species; therefore, new treatments are required. Immunocompromised patients have increased risk, as demonstrated by complications after BCG vaccination. On the other hand, idiopathic pulmonary fibrosis is a fatal disease, with no therapy available to modify course of the disease. Gamma interferon (IFN-γ) plays an essential role as main activator of cytokine secretion in macrophages, also showing a potent anti-fibrotic effects. To evaluate the adjuvant effect of IFN-γ on these three clinical scenarios, five clinical trials were carried out. Patients treated with IFN gamma had satisfactory response according to clinical, imaging and functional criteria since their first evaluations, significantly improving when compared to the control group receiving placebo in a study of pulmonary atypical mycobacteriosis. Fast sputum conversion was obtained in mycobacterial infections, including tuberculosis. In the idiopathic pulmonary fibrosis study, 75% of treated patients were considered as responders (improvement + stable). Here we report the cases of two nursing babies with suppurative regional lymphadenitis caused by BCG, who were successfully treated with recombinant human IFN-γ. Treatment was well tolerated, with most of the adverse reactions corresponding to classical flu-like symptoms produced by the cytokine. We can conclude that IFN-γ is useful and well tolerated as adjuvant therapy in patients with pulmonary mycobacterial diseases or idiopathic pulmonary fibrosis.

Keywords: Interferon gamma, Mycobacteria, multidrug-resistant pulmonary tuberculosis, Mycobacterium avium complex, Idiopathic Pulmonary Fibrosis, BCG, lymphadenitis

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RESUMEN

Interferón gamma recombinante en el tratamiento de enfermedades pulmonares y causadas por micobacterias. Existe una incidencia incrementada de cepas de *Mycobacterium tuberculosis* y de micobacterias atípicas resistentes a los antibióticos convencionales, lo cual hace necesario nuevos tratamientos. Tienen mayor riesgo los pacientes inmunodeprimidos, evidenciado en complicaciones luego de la vacunación por BCG. Por otra parte, la Fibrosis Pulmonar Idiopática es una enfermedad fatal, sobre la cual ninguna terapia actual modifica su curso. El interferón gamma (IFN-γ) juega un papel crucial en la respuesta inmune mediada por macrófagos y posee además un potente efecto antifibrótico, con aplicación potencial en estos tres escenarios clínicos, por lo que se estudió su papel en la terapéutica de estas enfermedades como adyuvante a la quimioterapia establecida en 5 estudios clínicos. Se observó mejoría clínica, funcional e imagenológica en los pacientes tratados con IFN-γ desde las primeras evaluaciones, significativamente mejor que un grupo control que recibió placebo en el estudio de Micobacteriosis atípica. Hubo rápida conversión a negativo de los esputos en estas infecciones pulmonares y en tuberculosis. En el estudio de fibrosis pulmonar idiopática se logró mejorar o estabilizar la enfermedad en el 75% de los pacientes tratados. Se reporta por primera vez el tratamiento de linfadenitis supurada causada por BCG en lactantes. El producto fue bien tolerado; la mayoría de las reacciones adversas se relacionaron con el síndrome seudogripal típico del IFN-γ, ninguna considerada como grave. Se concluye que el IFN-γ es eficaz y seguro como terapia adyuvante en pacientes con enfermedades pulmonares causadas por micobacterias y en la fibrosis pulmonar idiopática.

Palabras clave: Interferón gamma, Micobacteria, tuberculosis pulmonar quimiorresistente, complejo Mycobacterium avium, Fibrosis Pulmonar Idiopática, BCG, linfadenitis

*I*ntroduction

In the last years, treatment with gamma interferon (IFN-γ) has been proposed as potentially effective in infectious and non-infectious human diseases, such as tuberculous and non-tuberculous mycobacterial infections, idiopathic pulmonary fibrosis (IPF; a progressive and lethal lung inflammation characterized by fibrotic response) and also in complications of Bacillus Calmette-Guerin (BCG) vaccination.

Gamma interferon is a cytokine produced by T helper-1 lymphocytes and NK cells. Its effects on macrophages is crucial for intracellular mycobacterial killing, as evidenced in animal models, such as: pro-

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duction of tumor necrosis factor alpha, reactive oxygen species and nitric oxide; increased expression of major histocompatibility complex surface antigens, Fc receptors display and intracellular concentration of some antibiotics; and decreased lysosomal pH [1].

Mutations in the IFN-γ receptor genes (*IFNGR1* and *IFNGR2*) are associated with frequent recurrence or the most serious forms of mycobacterial disease [2]. Patients defective in the production of IFN-γ or other cytokines or partially deficient of IFN-γ receptors can benefit from IFN-γ treatment [3]. Additionally, patients with serum anti IFN-γ autoantibodies are highly susceptible to mycobacteriosis [4].

Tuberculosis (TB) remains as an unresolved health problem worldwide. Two million people die annually due to non-AIDS related TB, which is the highest number of deaths attributable to a single infectious agent. The emergence of drug resistant (DR) or multidrug-resistant (MDR) strains has increased its global morbidity and mortality [5]. According to previous uncontrolled studies, treatment with aerosolized IFN-γ of five patients with MDR-TB resulted in clinical and bacteriological improvement and tolerability [6]. In another study, IFN-γ inhalation therapy may be effective for some cases of refractory MDR-TB otherwise unresponsive to conventional therapy [7].

On the other hand, prevalence of infections by atypical *Mycobacteria* (also called non-tuberculous *Mycobacteria*) is growing and suspected as surpassing *M. tuberculosis* incidence in some geographic areas. *Mycobacterium avium* complex (MAC) species are the most frequent, intrinsically resistant to anti-TB antibiotics. Fifteen patients with dissemi-nated MAC and other non-tuberculous mycobacteria infections were treated subcutaneously during one year or more, 13 of them improved and 7 had even apparent disease eradication [8]. Other groups of immunocompromised patients infected with *M. avium* received clinical and bacteriological benefits of this treatment as well [9].

In the case of IPF, half of the patients commonly die 4-5 years after the diagnosis and only 20% survive for 10 years. The recommended combined treatment with corticosteroids and immunosuppressive drugs do not improve the course of the disease, neither stop progression of the fibrosis, and these drugs are associated with high toxicity. It is known that IFN-γ inhibits lung fibroblast proliferation and chemotaxis and reduces collagen synthesis. Furthermore, this protein is a potent antagonist of transforming growth factor beta (TGF-β), a cytokine directly involved in severe lung fibrosis progression, and it also contributes to tissue repair and remodeling [10]. All this suggested that IFN-γ could be applicable to treat this condition. The first report about the use of IFN-γ in IPF demonstrated a considerable clinical improvement in these patients treated for a year, compared to those that received placebo [11]. Afterwards, a multinational phase III study was carried out, but no significant improvement was observed in progression-free survival, pulmonary functionality or quality of life. Nevertheless, patients with an initial less-deteriorated pulmonary function showed better survival [12]. Other authors indicate that IFN-γ can slow or arrest the loss of lung function, increase longevity and make lung transplantation possible [13]. Recent results showed that long-term treatment with this cytokine may improve survival and clinical outcome in patients with mild-to-moderate IPF [14].

Complications due to BCG vaccination are rare and generally associated to some congenital immunodeficiency. Observed lesions include abscesses and regional lymph nodes enlargement and ulceration, among other symptoms [15]. Genetic defects in IFN-γ or its receptors could result in alterations of macrophage-lymphocyte interactions in response to BCG. Patients with disseminated BCG often present defects in the production or action of IFN-γ and other cytokines [3].

In this work we show evidences on the adjuvant use of recombinant IFN-γ (Heberon Gamma R®) in patients with drug-resistant tuberculosis, pulmonary atypical mycobacteriosis and IPF. We also report two nursing babies with suppurative regional lymphadenitis caused by BCG who were successfully treated with this cytokine.

Results

Clinical trials of gamma interferon as adjuvant in patients with drug-resistant pulmonary tuberculosis

Cuban study

An open-label, non-randomized, non-controlled, pilot trial was carried out [16]. The study population was eight patients of both genders, 27-to-54-years-old, diagnosed with TB without showing a favorable response to the usual therapy and identified as pulmonary DR-TB cases in the country during the inclusion period. One intramuscular dose of 10^6 IU human recombinant IFN-γ was administered daily for 4 weeks, and then three times a week for the next 20 weeks. They received anti-TB drugs (WHO schemes) according to the resistance detected in each case by the antibiogram. Evaluations were carried out at the beginning and monthly during the study. A complete physical examination was done, with sputum samples collected for acid-fast-bacilli smear and culture, and thorax radiographies were recorded. Complete response to treatment was defined as the total disappearance of all signs and symptoms, negative sputum acid-fast-bacilli smear and culture, and resolution of pulmonary lesions as detected by X-rays. Partial response included decreased signs and symptoms, negative sputum smear and culture and stable X-ray lesions. No response was considered on persistence of signs and symptoms, positive bacteriological examinations, and lesions stabilization or progression.

Adverse events were mild, except for one moderate fever, and a fast favorable evolution was achieved (Table 1). The treatment with IFN-γ was well tolerated.

All respiratory signs and symptoms (except for finger clubbing) disappeared in all patients and body mass index increased in all but one. Sputum acid-fast-bacilli smears and cultures were negative within the first three months of treatment. All patients showed radiological improvement, with lesion size reduction, and total disappearance in one of them. The globular sedimentation rate (GSR) decreased in five out of six patients who had abnormal values at inclusion (data not shown). At the end of the IFN-γ treatment, all pa-

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Table 1. Six months follow-up data of eight Cuban DR-TB patients treated with IFN-γ

Patient*	1	2	3	4	5	6	7	8
Drug[a] regimen	A	B	A	A	B	A	B	B
Gain BMI (kg/m^2)	1.8	0.4	0.4	0.4	0.3	2.2	1.8	- 2.1[!]
Conversion time	2 mo.	3 mo.	3 mo.	1 mo.	3 mo.	2 mo.	2 mo.	3 mo.
Thorax X-ray	Residual fibrosis	Reabsorption and residual fibrosis	Residual bilateral fibrosis	Lesions resolution	Residual fibrosis	Lesions size reduction	Residual fibrosis	Lesions size reduction
GSR (mm/h)	5	48	26	40	42	20	23	77

*Sputum smears and culture status were negative for all the patients.
[!] Loss of body weight
[a]Drug regimens were A) ethambutol, ethionamide, pyrazinamide, ciprofloxacin and kanamycin, except in patient 4 where kanamycin was substituted by amikacin; and B) rifampin, ethambutol, pyrazinamide and kanamycin. Mycobacteria treated with drug regimen A were resistant to isoniazid, streptomycin and rifampin; and to isoniazid and streptomycin that in regimen B.

tients were evaluated as complete responders. Seven of them remained bacteriologically, clinically and radiologically negative at least twelve months after the end of treatment.

At the same hospital, 19 DR-TB cases were treated with chemotherapy only, for five years prior to the present study. None of them reached culture conversion after three months of treatment with chemotherapy, and less than half converted after six months. They also showed worse clinical outcome (data not shown).

Indian study

The design, selection, treatment, evaluation and follow-up of the patients were similar to that of the Cuban study. Ten twenty nine years old patients, half of them men, were included. All of them were resistant to rifampicin and isoniazid. They steadily increased their body weight, reaching the level of statistical significance at the end of treatment ($p = 0.0001$; 24 weeks), when a remarkable mean increase of approximately 6 kg was recorded. There was an improvement in hemoglobin from 10.9 at entry to 12.5 g/dL at week 24. Damage in the left lung was significantly reduced ($p = 0.039$), around the double at the end of treatment. Damage in the right or in both lungs was reduced but not significantly. A complete clinical and radiological response was obtained in more than 60% of the patients, who showed mild or moderate adverse events, predominantly headache (50%).

Clinical trial of adjuvant interferon gamma in patients with pulmonary atypical mycobacteriosis: a randomized, double-blind, placebo-controlled study

A randomized, double-blind, placebo-controlled trial was carried out at the "Benéfico Jurídico" Hospital, which is the national reference unit for mycobacterial and other respiratory diseases. Another participating institution was the "Amalia Simoni" Hospital [17]. Thirty-two patients of more than 18 years old were studied. They were diagnosed with atypical mycobacteriosis, by isolation and classification of atypical mycobacteria species in sputum-culture samples, showing symptoms such as cough, expectoration, and tuberculosis-like pulmonary lesions at thorax radiography. Patients were randomly distributed in two groups of IFN-γ as adjuvant to oral chemotherapy (IFN-γ group, N = 18) or chemotherapy plus placebo (placebo group, N = 14). They were treated with 10^6 IU of human recombinant IFN-γ or placebo intramuscularly administered daily for 4 weeks, and then 3 times a week for the next twenty weeks. All patients received the same oral conventional antibiotic schedule daily as it follows: azithromycin, 500 mg; ciprofloxacin, 1 g; rifampin, 600 mg; and ethambutol, 2 g. The main outcome was an overall response that integrated clinical, bacteriological and radiological results, similar to that of DR-TB trials. Additionally, several immune response and oxidative stress markers were measured.

Both groups were homogeneous at the beginning: average age was 60 years, 75% men, 84% white; and MAC infection prevailed (94%). Treatments were well tolerated. At the end of treatment, 72% of patients treated with IFN-γ were evaluated as responders, but only 36% in the placebo group. The difference was maintained during the follow-up (Figure 1). A more rapid complete response was obtained in the IFN-γ group (5 months before), with a significantly earlier improvement in respiratory symptoms and pulmonary lesions reduction (Table 2). Disease-related deaths occurred in 35.7% of patients in the placebo group and only in 11.1% of the IFN-γ group. Three patients in the IFN-γ group normalized their globular sedimentation rate values. Although differences in bacteriology were not significant during the treatment, some patients in

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Table 2. Patients with pulmonary atypical mycobacteriosis. Times to responses in months. Data are expressed as mean (95% CI).

Treatment effect	Time of response IFN-γ N=18	Placebo N=14	P (log-rank)
Overall complete response	7.9 (4.6;11.4)	12.8 (9.2; 16.5)	0.024
Overall complete or partial response	6.4 (3.1; 9.7)	11.4 (7.0; 15.8)	0.050
Radiological improvement	4.3 (1.9; 6.7)	10.3 (6.2; 14.5)	0.003
Disappearance of symptoms	5.3 (2.4; 8.1)	10.4 (6.1; 14.8)	0.044
Disappearance of dyspnea	3.8 (1.2; 6.4)	8.6 (4.1; 13.2)	0.028
Sputum- Direct (negative)	3.9 (1.7; 6.1)	8.2 (3.6; 12.7)	0.105
Sputum- Culture (negative)	4.8 (2.1; 7.5)	8.2 (3.8; 12.5)	0.190
Disease-related deahts	20.6 (19.9; 21.4)	14.6 (10.7; 18.6)	0.053

the placebo group reconverted positive during the follow-up. Significant increase in serum TGF-β and advanced oxidation protein products were observed in the placebo group but not among patients treated with IFN-γ. Flu-like symptoms predominated in the IFN-γ group. No severe events were recorded.

Clinical trial of interferon gamma and decreasing-dose prednisone therapy in patients with idiopathic pulmonary fibrosis

A pilot, open label clinical trial was carried out to obtain first evidences of the efficacy and safety of a short-term IFN-γ treatment and decreasing-dose prednisone in patients with IPF. Twelve patients with IPF, as confirmed by histopathology, were treated for six months with 10^6 IU of recombinant human IFN-γ by intramuscular route, three times a week. A concomitant prednisone treatment was administered daily for a year. The dose was gradually reduced from 60 to 20 mg. Clinical, functional, and imaging evaluations were carried out before, and 3, 6 and 12 months after treatment.

Most of the patients showed clinical improvement; dyspnea, dry cough and crepitations disappeared notably. Three patients increased their forced vital capacity more than 12%, and just another one showed this magnitude decreased. Alterations in arterial gases were less frequent in the last evaluations. Fibrotic lesions were reduced in 5 out of 12 patients, one of them with complete remission. Seventy five percent of all the patients recruited were considered as responders (improvement + stable) at the end of IFN-γ treatment (month 6), while 58.3% remained as responders after the follow-up (month 12). Two patients died during the study, but only one was caused by the disease. The other ten patients remain alive up to date, some of them with 7-8 years of survival (Table 3). The treatment with IFN-γ was well tolerated, since mild to moderate flu-like adverse reactions predominated.

Suppurative lymphadenitis caused by BCG treated with recombinant interferon gamma. A two-case report

Two pediatric patients with adverse reactions induced by the BCG vaccine were presented, both showing suppurative and abscessed regional lymphadenitis, one month after birth [18]. After failed cycles of chemotherapy, they were treated with recombinant IFN-γ, intramuscularly, 50 000 IU/kg (up to 10^6 IU) daily during the first month, the frequency been sub-sequently reduced according to the progression of the disease. Case No.1 was a nursing girl with family history of tuberculosis that had suppurative axillary and supraclavicular adenopathies after BCG vaccination. She completely healed after 3 months of treatment with imperceptible lesions after 6 months. Case No.2 was a nursing boy without TB familiar antecedents but with more lesions given by suppurative axillary, infra and supraclavicular adenopathies. Only a non-suppurative small granuloma remained after one year of treatment, and all the lesions healed, taking skin pigmentation after 23 months of treatment.

Relevance of the studies

These results can improve human health, since these are serious illness that rebound threatening life of patients. In the case of lung diseases caused by *Mycobacteria*, the presence of extremely drug-resistant strains in some countries together with inadequate *directly observed therapy* (DOT) represent a serious health problem. An increment in the immune response due to adjuvant immunotherapy with IFN-γ can reduce the time of treatment, diminishing second-line drug toxicity and possible relapses or resistance to the new drug and the need for recessional surgery when treating extensive lesions, it could reduce the application of recessional surgery. The conversion of patients from infective to non-infective is a major achievement, allowing the reincorporation of patients to society.

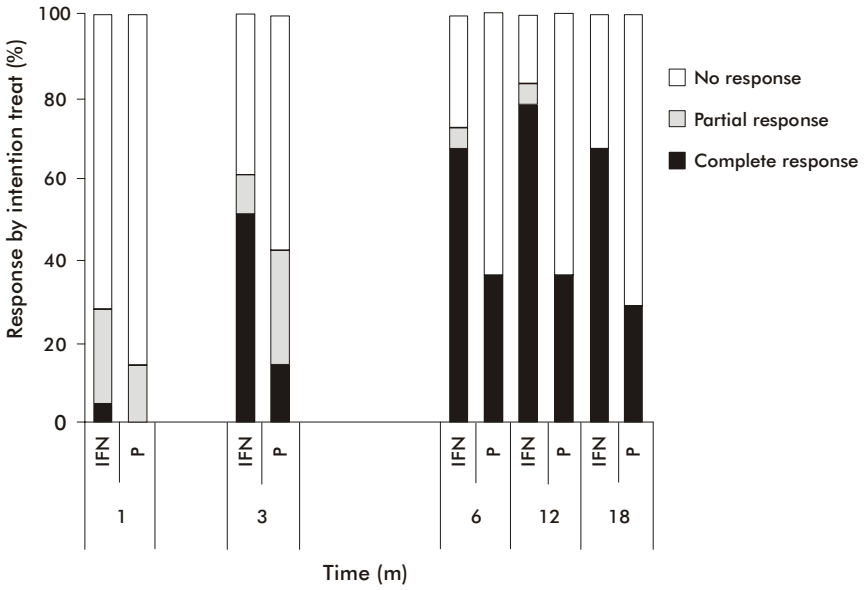

Figure 1. Patients with pulmonary atypical Mycobacteriosis. Graphic representation of the response (by intention to treat) to IFN gamma or placebo adjuvant to chemotherapy during the study. Time is expressed in months. Chemotherapy + IFN gamma (N= 18); Chemotherapy + Placebo (N= 14).

Results of the clinical trial of adjuvant IFN-γ in atypical mycobacteriosis shown are the first and largest randomized, controlled clinical study using an immunomodulatory agent systemically in an atypical mycobacterial infection. The antibiotic scheme of this trial was the best as recommended. Radiological response during treatment was the most significant benefit of IFN-γ. As mentioned, treating these mycobacterial infections is more difficult than the treating of tuberculosis, due to their high resistance to chemotherapy.

The combined treatment with IFN-γ and decreasing-dose prednisone can be highly beneficial in patients with IPF. Keeping in mind the progressive natural course of this illness and the ineffective (palliative) available drugs, we also considered those patients with stable disease as responders, since progression could be arrested. Many clinicians consider lung transplantation the only demonstrated effective therapeutic option, but its utility is obviously limited because of the patient's eligibility, morbidity and mortality of this procedure and organ supply. Relapses recorded during the follow-up can suggest a more prolonged IFN-γ treatment. Although efficacy of recombinant IFN-γ in IPF seems to be contradictory as reported [11-14], the do-

se level of prednisone (minimum 20 mg) was higher than in previous reports. This combination apparently shows better results in terms of efficacy in the advanced disease. Additionally, in our study all the responders reincorporated to society, some of them before the 6 months of treatment, leading to economic benefits. On the other hand, both children with suppurative lymphadenitis caused by BCG apparently healed with IFN-γ treatment, increasing the expectations in this sense.

Due to these successful results, the Cuban Regulatory Authority for Medicaments approved the use of IFN-γ to treat the abovementioned pulmonary diseases.

Table 3. Current status of the twelve patients with idiopathic pulmonary fibrosis

Patient	Inclusion date (d/m/y)	Status	Time of survival
HA-01	24/10/2000	Alive	8 ½ y
BJ-01	12/02/2001	Alive	8 y
BJ-02	18/09/2001	Alive	7 ½ y
BJ-03	01/02/2002	Alive	7 y
BJ-04	31/01/2002	Alive	7 y
BJ-05	06/02/2002	Alive	7 y
BJ-06	22/04/2002	Alive	7 y
BJ-07	29/01/2003	Alive	6 y
BJ-08	11/03/2003	Alive	6 y
BJ-09	04/02/2003	Died of cancer (Mesotelioma)	1 ½ mo.
BJ-10	13/05/2003	Died of IPF progression	1 ½ y
BJ-11	16/06/2003	Alive	6 y

Conclusions

The results shown in this report may justify the rationality of using IFN-γ as adjuvant for anti-mycobacterial drugs in patients with drug-resistant pulmonary tuberculosis or pulmonary atypical mycobacteriosis (mainly in MAC infection). Their combination could reduce treatment duration, toxicities and possible relapses. In some cases it could prevent recessional surgery. Further, more extensive, controlled clinical trials are encouraged to confirm this assessment. This cytokine could be a preferable option as anti-fibrotic agent in patients with idiopathic pulmonary fibrosis, and possibly to produce a marked improvement of lesions in pediatric patients with suppurative lymphadenitis caused by BCG.

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