

# Recombinant Interferon Gamma-1b and Low-Dose Steroid in Two Pediatric Cases of Nonspecific Interstitial Pneumonia

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## Abstract

We report two young girls, the first almost 18 years old and the second 12<sup>1</sup>/<sub>2</sub> years old, affected with nonspecific interstitial pneumonia, both diagnosed at the age of 11 by open lung biopsy and both being treated with low-dose steroid. Due to insufficient response to conventional therapy and based on positive therapeutic results following the use of subcutaneous recombinant interferon gamma-1b in fibrosing interstitial pneumonias of adults, they were given a 1-year trial of subcutaneous recombinant interferon gamma-1b in association with a steroid. Our experience with these two young patients suggests that interferon gamma-1b cannot be considered as stabilizing or a curative therapy to control or reverse nonspecific interstitial pneumonia unresponsive to steroids alone.

**Key Words:** Interferon gamma, steroid, nonspecific interstitial pneumonia, pediatrics.

## Glossary

ERV:	expiratory residual volume
FEV <sub>1</sub> :	forced expiratory volume in 1 second
FVC:	forced vital capacity
IFN:	interferon
NSIP:	nonspecific interstitial pneumonia
paCO <sub>2</sub> :	arterial carbon dioxide tension
paO <sub>2</sub> :	arterial oxygen tension
SVC:	slow vital capacity
Th 1:	T-helper type 1
Th 2:	T-helper type 2

## Introduction

NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP) is a chronic disorder of the lung characterized by inflammatory cell infiltration of the interstitium and fibrosis within the alveolar walls; these changes appear to be temporally and firmly uniform in most cases (1). The biologic scenario of fibrosing interstitial diseases is characterized by the shift of T lymphocytes in favor of the T-helper type 2 (Th 2) reaction, which is followed by reduced production of interferon (IFN) gamma, a main mediator of the T-helper type 1 (Th 1) reaction (2–4). The antifibrotic properties

of IFN gamma have been demonstrated to inhibit collagen synthesis *in vitro* and *in vivo* (5, 6). We have evaluated the possible beneficial effect of recombinant IFN gamma-1b for a 12-month period in two young girls with NSIP, who had received a constant low-dose steroid. Subcutaneous recombinant IFN gamma-1b (provided by Boehringer Ingelheim, Italy) was added to their regimen three times a week and oral low-dose prednisone was continued. IFN gamma-1b was used at an initial dosage of 100 µg and maintained until the third month, when it was increased to 150 µg and finally increased to 200 µg at the fifth month of treatment. Prednisone was used at a dose of 15 mg on alternate days. Methods and results of our investigation are reported.

## Patients and Methods

Patient 1, female, born full-term after normal pregnancy and delivery to a first gravid, complained of occasional dry cough and dyspnea with medium exertion (with otherwise normal vital signs), at the age of 11 years. Routine laboratory findings were unrevealing. Chest X-ray showed a diffuse thickening of the alveolar walls. Chest high-resolution computed tomography showed a predominantly subpleural distribution of reticular opacities with septal thickening. Spirometry revealed severely reduced slow vital capacity (SVC), 420 mL (18.1% predicted) (7). Blood gas analysis showed profound hypoxemia, with the paO<sub>2</sub> of 72 mm Hg (normal range 75–100) with maximal exertion. The paO<sub>2</sub> was normal at rest. Open lung biopsy

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showed NSIP (Fig. 1). She was started on prednisone (60 mg/m<sup>2</sup>/day). Pulmonary function remained unchanged. Prednisone was reduced to 15 mg on alternate days without interruption. Her condition appeared to be stable for five years. Thereafter, blood gas revealed a paO<sub>2</sub> of 68.3 mm Hg and paCO<sub>2</sub> of 45.4 mm Hg, normal range 35–45, breathing room air. A reduction of lung volumes occurred. Transbronchial biopsy and bronchoalveolar lavage were refused by the patient's relatives. After we had obtained an informed consent, when the patient was 17 years and 10 months, IFN gamma-1b therapy three times/week was proposed, combined with maintenance prednisone dose (15 mg on alternate days) for 1 year.

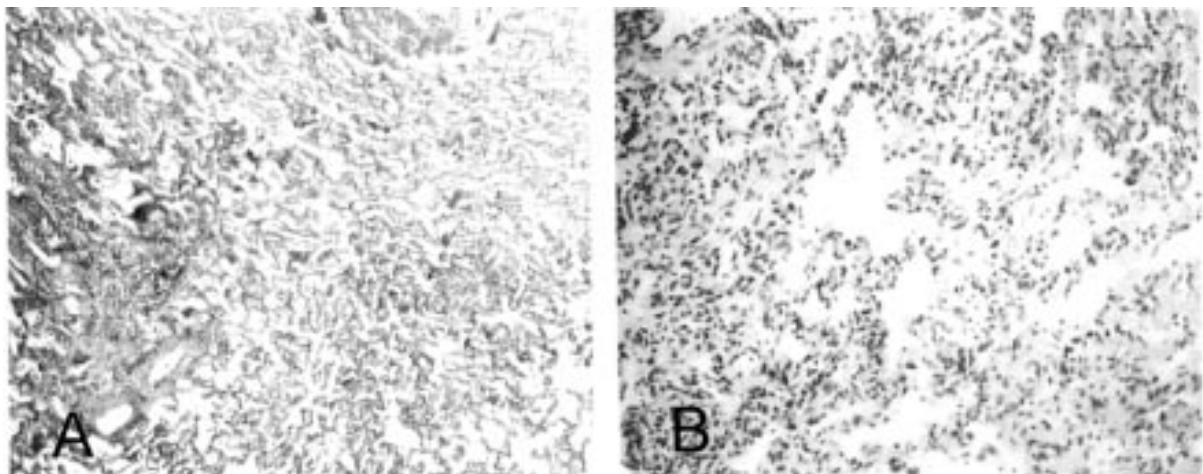
Patient 2, female, born full-term after uncomplicated pregnancy and delivery to a third gravid, complained that she was unable to climb one flight of stairs or walk to school. She noted cyanosis with exercise and digital clubbing at the age of 11 years. Typical respiratory symptoms, such as shortness of breath, emerged about 10 months after the first clinical evaluation. Chest radiograph revealed peripheral reticular opacities without cardiomegaly or hilar adenopathy (Fig. 2), and chest high-resolution computed tomography revealed a diffuse thickening of the interstitium. Echocardiography failed to show pulmonary hypertension. Spirometry revealed reduced SVC, 1240 mL (62.9% predicted) (7). Blood gas analysis showed paO<sub>2</sub> of 74 mm Hg, on maximal exertion, which reversed to normal with rest. Neither bronchoalveolar lavage nor gallium lung scintiscan confirmed an active inflammation.



**Fig. 2.** Chest AP X-ray from patient 2, revealing bilateral reticular infiltrates most prominent in the lower lobes, indicating chronic interstitial pneumonia.

Open lung biopsy revealed NSIP. Treatment included prednisone (60 mg/m<sup>2</sup>/day), slowly reduced to 25 mg on alternate days. She remained stable for about 1 year. At age 12 years and 6 months, IFN gamma-1b therapy three times/week combined with a maintenance dose of prednisone (15 mg on alternate days) was instituted and maintained for 1 year.

The table summarizes our assessment of SVC, expiratory residual volume (ERV), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV<sub>1</sub>), all expressed in mL, arterial oxygen/carbon dioxide tension (paO<sub>2</sub>/paCO<sub>2</sub>) at rest, expressed in mm Hg, and a six-minute walk test under conditions of standardized ergometry (with the distance covered dur-



**Fig. 1.** Percutaneous open lung biopsy from patient 1. In panel **A**, a low-power magnification, edema and fibrosis within alveolar septa and interstitial inflammatory infiltrates are apparent. In panel **B**, a high-power magnification, hyperplasia of type 2 pneumocytes and chronic inflammation prevalently characterized by lymphocytes can be recognized.

**TABLE**  
*Functional Measurements for the Two Patients*

	pre IFN g-1b	1 month	3 months	6 months	9 months	12 months
<b>Patient 1</b>						
SVC (mL) (% predicted)	760 (22)	980 (28)	740 (21)	780 (22)	640 (19)	560 (17)
ERV (mL) (% predicted)	480 (34)	580 (40)	480 (34)	450 (32)	130 (9)	160 (11)
FVC (mL) (% predicted)	1030 (28)	720 (20)	700 (19)	730 (20)	500 (15)	540 (16)
FEV <sub>1</sub> (mL) (% predicted)	430 (13)	450 (14)	450 (14)	430 (13)	310 (10)	340 (11)
paO <sub>2</sub> (mm Hg) at rest	68.3	68.7	76.7	69.9	63.8	75.8
paCO <sub>2</sub> (mm Hg) at rest	45.4	45.6	44.0	47.4	48.0	45.5
O <sub>2</sub> saturation at rest (%)	94.0	93.9	94.9	93.6	92.5	95.2
Distance covered (m)	250	300	300	230	330	300
O <sub>2</sub> sat. (%) after walking test	70–75	75–80	80–84	81	75–80	75
<b>Patient 2</b>						
SVC (mL) (% predicted)	1470 (67)	1510 (69)	1370 (57)	1390 (61)	1400 (62)	1150 (48)
ERV (mL) (% predicted)	410 (69)	490 (82)	410 (69)	480 (80)	540 (90)	500 (84)
FVC (mL) (% predicted)	1550 (64)	1560 (64)	1370 (57)	1360 (60)	1400 (62)	1150 (48)
FEV <sub>1</sub> (mL) (% predicted)	1410 (72)	1390 (71)	1220 (54)	1210 (57)	1250 (58)	1270 (59)
paO <sub>2</sub> (mm Hg) at rest	93.7	94	94.5	104.9	91.6	95.8
paCO <sub>2</sub> (mm Hg) at rest	33.8	34.5	32	28.3	32.5	33.1
O <sub>2</sub> saturation at rest (%)	95	95	94	97.9	96.9	97.4
Distance covered (m)	600	550	550	450	450	450
O <sub>2</sub> sat. (%) after walking test	88	86	87	82	90	90

ing the six minutes expressed in meters and oxygen saturation during the same time expressed in %) (8). Examinations took place prior to the beginning of treatment, after one month, and then every three months during the year of observation. Improvement of pulmonary function was defined as a 10% increase in predicted value of SVC, ERV, FVC and FEV<sub>1</sub> or a 3% increase in oxygen saturation with the same fraction of inspired oxygen, resting or after exertion.

### Discussion

The efficacy of any treatment for chronic interstitial pneumonias has been shown to be related to strict histological criteria (9). NSIP generally displays a relatively quiescent fibrosis, but sometimes the mixture of persistent inflammation and active fibroblast proliferation appears to worsen, so that NSIP might resemble the clinical features of usual interstitial pneumonia (10). There are good theoretical reasons why IFN gamma-1b might be beneficial in fibrosing interstitial pneumonias. Moreover, supporting evidence comes from studies demonstrating that interferons, especially IFN gamma, a major Th1 cytokine, have profound suppressive effects on the synthesis of extracellular matrix, inhibiting both fibroblast and chondrocyte collagen production *in vitro* as well as decreasing procollagen gene transcription *in vivo* (11–13). When

fibrosis is not completely established, further progression could be prevented by IFN gamma therapy, helping the shift of cytokine expression toward a more normal Th1/Th2 balance (14). The first positive results are attributed to Ziesche et al., who treated 9 adult patients with idiopathic pulmonary fibrosis, with IFN gamma-1b and prednisolone. Significant benefits were observed in the physiological parameters (15). The decision to treat our two young patients with subcutaneously injected IFN gamma-1b plus oral steroid was based on these results, and our assumption that NSIP belongs to the group of fibrosing pneumopathies and that its natural history may in some way become more aggressive with a tendency to massive lung fibrosis.

Both patients completed the study. The main side effects from IFN gamma-1b administration were fever in the first month of treatment in both patients and sporadic dizziness in patient 1. During the last months of the trial an increasing muscular weakness with fever emerged in both. Acetaminophen was prescribed.

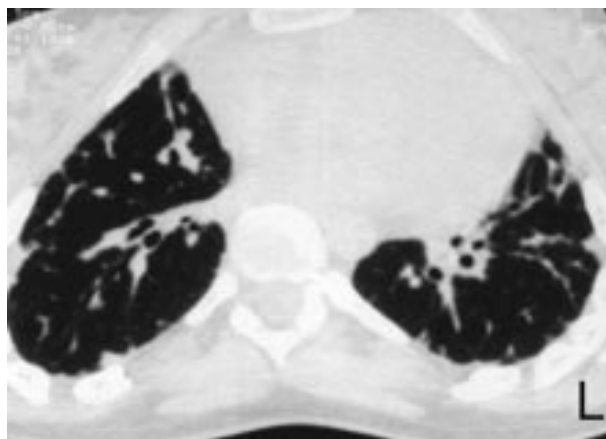
No improvement was noted in our patients. We recorded only a partial response of SVC in the first month of treatment, while FVC and FEV<sub>1</sub> in both patients decreased. Blood gases at rest, distances covered during the walk test, and oxygen saturation remained unchanged for both patients during the observation period. Nor did high-resolution computed tomography per-

formed at the beginning and at the end of the study show any improvement. On the contrary, it revealed patches of "ground-glass" areas alternating with normal areas of the lung in patient 1 (Fig. 3). Right ventricular ejection fraction measured by echocardiography prior to the study, at six months, and at the end of treatment remained unchanged.

There are several possible explanations for our patients' lack of response to treatment. The effectiveness of IFN gamma-1b has been demonstrated in only a single preliminary study related to idiopathic pulmonary fibrosis. The range of IFN gamma bioactivity is rather wide and its action may prove to be nonspecific. Only 2 pediatric patients were studied. Any effect of IFN gamma might depend on the extent of fibrosis in NSIP. And finally, initial lung functional tests may be insufficient to predict the extent of response to treatment. Nonetheless, it is possible that progression of the disease may have been retarded by IFN gamma, but longer clinical follow-ups and histologic evidence would be required to make such a judgment. However, from this experience with two pediatric patients, IFN gamma cannot be considered effective treatment for patients with NSIP. The exact role of IFN gamma-1b in the treatment of pediatric NSIP or other fibrosing interstitial pneumonias needs to be determined by large, multicenter, clinical efficacy trials.

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**Fig. 3.** A representative high-resolution CT scan of the thorax from patient 1 after the conclusion of the trial, showing patches of intralobular linear opacities and irregularly thickened septa which alternate with normal-appearing areas.

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