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Another "chance" for Interferon gamma 1b?

G.L. Casoni[1], M. Chilosi[2], M. Romagnoli[1], S. Tomassetti[1], V. Poletti[1]

[1] Thoracic Department, Morgagni-Pierantoni Hospital, Forlì, Italy; [2] Department of Pathology, University of Verona, Italy

The treatment of Idiopathic Pulmonary Fibrosis (IPF) with interferon-gamma (IFN-γ)1b is a therapeutic option that has been used in the largest group of patients; nonetheless, its efficacy remains controversial, although a differential effect in specific subgroups of patients has been postulated (1). Recently Luppi et al. (2) suggested that individual susceptibility could determine clinical response to treatment with IFN-γ in patients with IPF.

Methods

We conducted a retrospective study of clinical functional and pathological data of patients already classified as affected by IPF/Usual Interstitial Pneumonia (UIP) that obtained clinical, functional and radiological benefit after treatment with IFN-γ1b (4 out of a total of 10 treated patients). These patients have been treated for at least 6 months with IFN-γ1b (200 μg/die subcutaneously three times a week), accordingly to the indications of the Italian Drug Agency.

Prior to treatment with IFN-γ1b, all 10 patients were treated with systemic steroids (prednisone) without getting any clinical benefit. All patients continued to receive low-doses of systemic steroids (up to 10 mg daily) during treatment with IFN-γ1b,

Results

4 patients showed an overall improvement of respiratory function (Figure 1) and stability of the clinical and radiological findings at the end of treatment. The major functional improvements there were in those who started IFN-γ1b at early symptoms (patients with less advanced disease in particular radiologically). In improved patients, a more careful pathological revaluation of available surgical lung biopsy (3 patients out of 4) showed a pathological picture consistent with UIP pattern in chronic hypersensitivity pneumonia (HP), an histological finding characterized by fibrosis with also centrilobular involvement, presence of scattered interstitial micro-granulomas (better depicted using the immunohistochemical marker cathepsin-K) (3) and focal bronchiolisation. Finally, serum specific precipitating antibodies resulted positive in 2 patients out of 4.

Comment

A possible explanation of therapeutic effect of IFN-γ1b in these patients might be that chronic HP is characterized by an excess of profibrotic cytokines and by a relative deficiency of interferon-γ. As sug-

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Correspondence: Venerino Poletti,
Dipartimento Toracico, Ospedale GB Morgagni,
Via Forlanini 34, 47100 Forlì, Italy
Tel. ++39-0543-735830
Fax ++39-0543-735882
E-mail: venerino.poletti@gmail.com

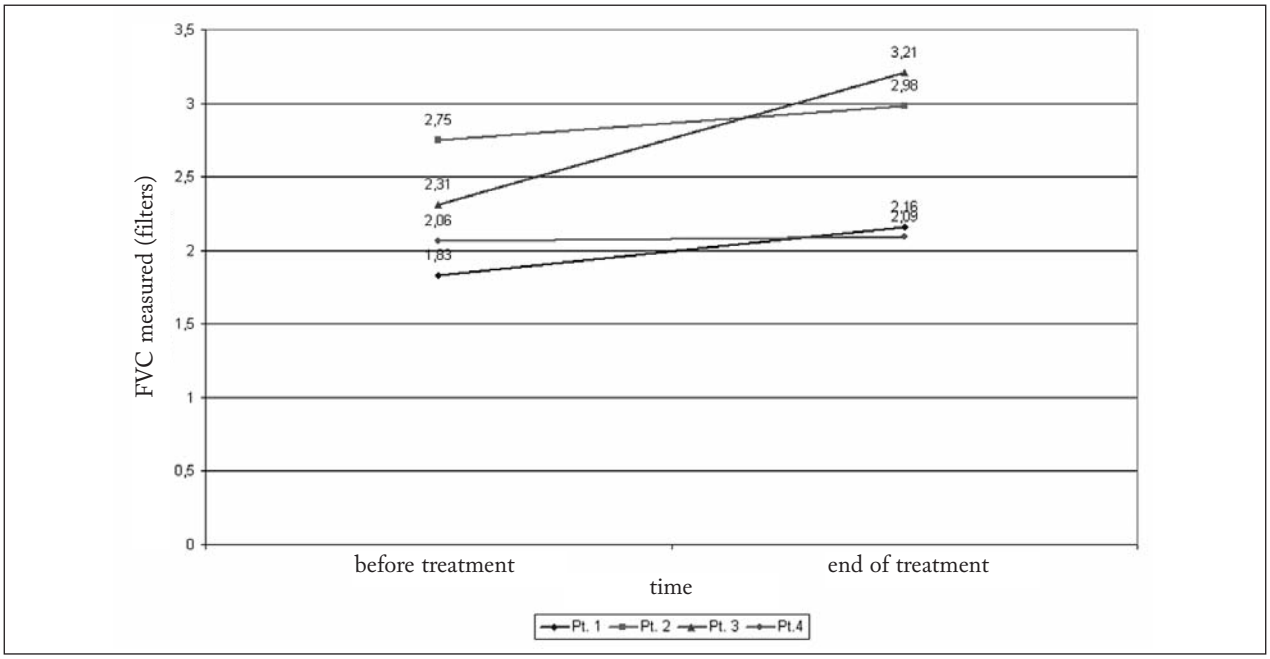

Fig. 1. Change in forced vital capacity (FVC) during treatment with IFN-γ1b

gested by Ziesche R et al. (4) exogenous interferon gamma therapy might inhibit the expression of profibrotic cytokines. Accordingly, it has been recently demonstrated that chronic HP patients lose effector T-cell function and exhibit skewing towards Th2 activity (5), which may be implicated in the fibrotic response that characterizes this clinical form. Therefore, IFN-γ1b could influence the course of chronic HP through anti-fibrotic and anti-inflammatory effects. However longer and larger studies are needed to investigate this particular hypothesis. Finally the initial misleading diagnosis of IPF (4 out of a total of 10 treated patients) is not surprising that much. In fact, it has already been shown that there is over 50% of inter-observer variation between pathologists related to the diagnosis of non-specific interstitial pneumonia and, in particular, its distinction from UIP (in the chronic HP, the interstitial inflammation may progress to irreversible scarring, including dense fibrosis with honeycombing and fibroblastic foci compatible with the histologic diagnosis of UIP) and that there is a spectrum (including chronic HP) of misleading thin-section computed tomographic (CT) diagnoses in patients with biopsy-proved IPF. Therefore, in view of this finding, it is very important to stress the need an interactive approach between clinicians, radiologists, and pathologists to improve the interobserver agreement.

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