

Brief communication

Treatment with IFN- α in corticosteroid-unresponsive asthma

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Key words: IFN- α , asthma, corticosteroid

Many patients with bronchial asthma can be successfully treated with corticosteroids. However, a subgroup of patients does not respond to either topical or systemic corticosteroid therapy; they are called corticosteroid-unresponsive or resistant asthmatics. There have been clinical studies with immunosuppressive drugs such as cyclosporin A, methotrexate, or anti-CD4 mAb with limited success in these severe asthma cases. We treated one patient with severe corticosteroid-unresponsive asthma with IFN- α , which has successfully been used in treating patients with the hypereosinophilic syndrome.¹ The reported case suggests that IFN- α may, besides possible direct antiasthmatic effects, increase corticosteroid sensitivity.

CASE REPORT

A 38-year-old woman with a history of hay fever followed by allergic asthma had been treated since 1977 for aspirin-induced asthma associated with polyposis nasi. Because of poor clinical control of her asthma, systemic corticosteroid therapy was initiated in 1980. In an attempt to reduce the daily corticosteroid dose, a methotrexate therapy (15 mg per week) was additionally introduced in 1990, but it proved to be ineffective and was therefore discontinued 2 years later. Although the patient received 100 mg of prednisolone per day, frequent episodes of sudden pulmonary crisis, diarrhea, vomiting, generalized patchy erythema, and marked blood eosinophilia (1300–2900/mm³) without leukocytosis or lymphocytosis were observed. An immunohistologic investigation of a bone marrow biopsy specimen taken during a time of blood eosinophilia demonstrated increased numbers of eosinophils. The investigation of the bronchoalveolar lavage fluid revealed 16% eosinophils, suggesting eosinophilic infiltration of the lungs. Because of the uncon-

trolled clinical situation, 150 mg of cyclosporin A was given in addition to the 100 mg prednisolone daily in 1996. The clinical situation remained unchanged and therefore the cyclosporin A therapy was discontinued after 9 months. Table I shows the situation of the patient at this time (October 1996). Because of uncontrolled asthmatic symptoms, the patient has been treated with low-dose IFN- α and immunologically monitored during this therapy.

METHODS

Immunophenotyping of blood lymphocytes, IL-5 measurements, and lymphocyte proliferation assays were performed by standard protocols as previously described.^{2–4}

RESULTS AND DISCUSSION

Immunophenotyping of blood lymphocytes revealed no evidence of a clonal population of aberrant T cells as a possible cause of the persistent eosinophilia (Table I).^{2,3} Normal corticosteroid-dependent effects such as relative neutrophilia, lymphopenia, eosinopenia, decreased HLA-DR expression on monocytes,⁴ or decreased proliferative response of peripheral blood T cells after stimulation with an anti-CD3 mAb were not seen, suggesting a state of corticosteroid resistance in this patient. A therapeutic trial with the leukotriene receptor antagonist zafirlucast (20 mg twice daily) did not change the situation and was discontinued after 6 months. The daily prednisolone dose needed to control symptoms reached 500 mg at this time (September 1997).

In October 1997, a low-dose IFN- α 2a (Roferon, 3×10^6 IU/d) therapy was initiated, but it proved to be inefficient in controlling clinical symptoms and eosinophilia. The dose was therefore increased to 7.5×10^6 IU per day for 2 weeks. This resulted in relative neutrophilia, lymphopenia, and eosinopenia (Table I, November 1997). The proliferative response of peripheral blood T cells and their release of IL-5, a cytokine that controls eosinophil differentiation, were markedly decreased.

The patient was then treated with 6×10^6 IU per day IFN- α for an additional 6 months. Although a stepwise reduction of the prednisolone dose was followed, a cushingoid habitus developed. Serum morning cortisol levels indicated significant suppression of the adrenal gland. Immunologic analysis at the end of this period (Table I, May 1998) demonstrated that the patient remained in an immunosuppressive state with an additional reduction of the HLA-DR expression on monocytes. Together, these data suggested that the patient was no longer corticosteroid unresponsive.

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Supported by Swiss National Science Foundation grant No. 32-49210.96 and the Foundation of Scientific Research of the University of Zurich. S. G. was supported by the Doehrenkamp Foundation.

Received for publication Oct 12, 1999; revised Dec 28, 1999; accepted for publication Dec 28, 1999.

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J Allergy Clin Immunol 2000;105:1035–6.

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0091-6749/2000 \$12.00 + 0 1/54/105317

doi:10.1067/mai.2000.105317

TABLE I. Clinical and laboratory evaluation before and during therapy with IFN- α

	October 1996	November 1997	May 1998	August 1998	May 1999
Antiasthma treatment					
Prednisolone (mg/d)	100	190	130	50	20
Cyclosporin A (mg/d)	150	0	0	0	0
IFN- α (10^6 IU/d)	0	7.5	6	3	3
Lung function					
FEV ₁ (L)*	1.76	2.15	2.88	2.90	2.69
Differential blood leukocyte count					
Leukocytes (/mm ³)	8,600	9,500	8,840	5,750	5,840
Lymphocytes (%)	36.5	13.5	9.5	21.0	44.3
Eosinophils (%)	21.0	0	0	2.0	0.2
Neutrophils (%)	33.0	79.0	86.5	63.0	43.0
Monocytes (%)	9.5	7.5	4.0	14.0	12.5
Differential blood lymphocyte count					
CD3+ T cells (%)	72.6	63.1	67.2	68.6	76.1
CD19+ B cells (%)	1.3	2.1	5.0	1.5	2.6
CD3- CD16+ natural killer cells (%)	18.8	25.0	25.7	22.3	18.9
CD4/CD8 ratio	2.0	1.9	2.3	2.3	2.2
HLA-DR antigen on monocytes†					
CD14+ HLA-DR+ (%)	92.6	97.8	84.2	89.1	94.9
Lymphocyte transformation test‡					
No treatment (counts/min)	2,388	7,485	14,997	3,106	1,407
Anti-CD3 mAb (counts/min)	113,539	29,635	26,674	162,985	68,739
Stimulation index	47.5	4.0	1.8	52.5	48.9
IL-5§					
PBMCs (pg/mL)	90.0	41.0	<25.0	ND	<5.0
Morning serum cortisol					
Cortisol (ng/mL)	100.9	ND	25.0	23.0	24.3

ND, Not done.

*The normal FEV₁ for this patient is 2.83 L.

†HLA-DR expression on monocytes on control individuals was >92%.

‡This test was performed as described.² Stimulation index is ratio between counts per minute of anti-CD3 mAb stimulated and unstimulated PBMCs. This index is >20 in control individuals.§PBMCs were cultured at 10^6 /mL for 24 hours. IL-5 was detected in harvested culture supernatants by ELISA. Supernatants from control individuals did not contain measurable amounts of IL-5.

||Normal range of morning serum cortisol levels is 70-250 ng/mL. First indicated value is from May 1997.

IFN- α therapy has previously been associated with side effects even when only low doses were administered.⁵ In this study, at a dose of 6×10^6 IU per day, the patient had headache and vomiting. We therefore reduced the therapeutic dose of the cytokine to 3×10^6 IU per day, which was well tolerated. Despite concurrent reduction of the prednisolone dose, the asthma remained stable and the eosinophil counts never increased above 120 per cubic millimeter in the blood. With the reduction of the corticosteroid treatment, steroid-mediated immunosuppressive effects such as relative lymphopenia, decreased proliferative T-cell response in vitro, and reduced monocyte HLA-DR expression disappeared (Table I, August 1998 and May 1999). Further studies should be performed to evaluate the role of IFN- α as a new drug for these patients with severe asthma. In addition, the efficacy of IFN- α in different subgroups of patients with corticosteroid-unresponsive asthma should be investigated.

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