

## Original article

# Clinical and immunological effects of low-dose IFN- $\alpha$ treatment in patients with corticosteroid-resistant asthma

**Background:** Interferon (IFN)- $\alpha$  is a cytokine that possesses potent anti-viral and immunoregulatory activities. We aimed to assess clinical and immunological effects of low-dose IFN- $\alpha$  in patients with severe corticosteroid-resistant asthma with and without Churg–Strauss syndrome. There is currently no efficient pharmacological treatment available for this group of patients.

**Methods:** We studied 10 patients with corticosteroid-resistant asthma, in which  $3 \times 10^6$  IU/day IFN- $\alpha$  were administered in addition to the prednisone dose given already before introduction of the cytokine therapy. The prednisone dose was gradually reduced dependent on the clinical situation and used as a clinical readout to evaluate the efficacy of the cytokine therapy. To distinguish between IFN- $\alpha$ - and prednisone-mediated immunological changes, the corticosteroid dose was kept constant for at least 2 weeks upon introduction of the cytokine therapy in seven patients. The effects of treatment on clinical and immunological parameters were measured at 2–4 weeks and 5–10 months depending on the availability of the patient.

**Results:** Interferon- $\alpha$  treatment rapidly improved the clinical situation as assessed by lung function parameters and required prednisone dose. Important immunological changes included: decreased leukocyte numbers, increased relative numbers of CD4<sup>+</sup> T cells, increased differentiation of T helper (Th)1 cells, and increased expression of interleukin (IL)-10 in peripheral blood mononuclear cells.

**Conclusion:** Interferon- $\alpha$  treatment was associated with dramatic improvements in the condition of patients with corticosteroid-resistant asthma with and without Churg–Strauss syndrome. Potential mechanisms of action include the establishment of a correct Th1/Th2 balance and the induction of the anti-inflammatory IL-10 gene.

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Bronchial asthma is a chronic inflammatory disease, which is usually treated by inhaled corticosteroids and  $\beta_2$ -agonists (1). Such treatment is effective in the majority of patients with asthma, but a subgroup of patients does not respond well to these therapies and requires the systemic application of corticosteroids (2). However, some of these corticosteroid-dependent patients develop an even more severe asthma that is more or less corticosteroid unresponsive. In this patient group, the asthmatic disease frequently progresses into Churg–Strauss syndrome (allergic angiitis and granulomatosis) most likely due to insufficient suppression of the eosinophilic inflammatory response (3). No efficient therapy is currently available for such corticosteroid-resistant patients.

Interferon (IFN)- $\alpha$  is a cytokine that was originally believed to be an anti-viral factor. However, in recent years, it became clear that IFN- $\alpha$  has multiple actions on the immune system too (4). Interferon- $\alpha$  is usually used to treat patients with certain benign neoplastic (5) and viral

diseases (6, 7). Interferon- $\alpha$  was also successfully applied in patients with the hypereosinophilic syndrome that had been resistant to corticosteroids (8) and in patients with Churg–Strauss syndrome (9–11). Moreover, as there is evidence that IFN- $\alpha$  promotes T helper (Th)1 differentiation *in vitro* (12), it may represent a therapeutic option in diseases associated with increased Th2 activation, such as bronchial asthma.

After collecting some experience in treating single severe asthmatic patients with IFN- $\alpha$  (13), we designed a preliminary study with 10 patients to confirm the clinical efficacy of this cytokine therapy in asthma and to describe changes in the numbers of immune cells in blood as a consequence of this therapy. We also monitored spontaneous and stimulated cytokine production of peripheral blood mononuclear cells (PBMC) in a subgroup of four patients to better understand the potential molecular mechanism(s) by which IFN- $\alpha$  improves severe corticosteroid-resistant asthma.

Table 1. Baseline characteristics of patients

Patient no.	Sex	Age (years)	FEV <sub>1</sub> (% predicted)	Churg–Strauss syndrome	Blood eosinophils (%)	ECP ( $\mu$ g/l)	IgE (kU/l)	Prednisone/day (mg)
1	Female	24	57	No	0	5.5	2	150
2	Female	26	66	No	0	14.2	201	150
3	Female	43	37	Yes	5	12.5	281	30
4	Female	47	48	No	13	77.6	147	40
5	Male	40	26	No	0	nd	nd	60
6	Female	31	50	No	0	5.3	422	80
7*	Female	48	49	No	0	8.8	31	60
8*	Female	28	69	No	0	nd	243	120
9*	Female	55	60	Yes	1	8.0	3.3	125
10*	Female	48	38	Yes	5	11.5	723	40

\* Patients involved in cytokine study.

FEV<sub>1</sub>, forced expiratory volume in 1 s; ECP, eosinophil cationic protein; IgE, immunoglobulin E; nd, not determined.

**Materials and methods**

**Patients**

We studied 10 patients (nine female and one male) with severe steroid-resistant asthma (Table 1). Three of these 10 patients fulfilled the criteria of Churg–Strauss syndrome (14). All patients had unstable asthma and three patients had increased numbers of blood eosinophils in spite of receiving high amounts of systemic corticosteroids. At the time of the study, patients did not receive additional immunomodulators or leukotriene receptor antagonists. The forced expiratory volume in 1 s (FEV<sub>1</sub>) was <70% of predicted normal in each case. The patients were hospitalized for at least 6 weeks and again monitored 5–10 months after initiation of the cytokine therapy. The study was approved by the Swiss Academy of Medical Science represented by the medical ethics committee of Davos.

**Study design**

A dose of 3×10<sup>6</sup> IU/day recombinant IFN- $\alpha$  2a (Roferon A<sup>®</sup>, Roche, Basel, Switzerland) was administrated when the therapy was initiated. This dose was maintained in case of satisfactory efficacy and in the absence of major side effects for at least 5 months. The systemic corticosteroid treatment was maintained until a clinical improvement was seen and then gradually reduced. Spirometry, hematology, and eosinophil cationic protein (ECP) levels were measured within the first 4 weeks of treatment at least one time per week. Immunophenotyping of blood lymphocytes was performed before treatment and then two times under IFN- $\alpha$  therapy. The first immunological control investigation was performed within 2–4 weeks and the second between 5 and 10 months after initiation of therapy in all patients. Except in the first three patients, the systemic corticosteroid dose was kept unchanged until the first immunological control investigation in order to understand specific IFN- $\alpha$ -mediated mechanism(s). In four of these seven patients, cytokine expression was studied in PBMC.

**Immunomonitoring**

Immunophenotyping of blood lymphocytes and monocytes, cytokine measurements, and lymphocyte proliferation assays were performed by using standard protocols as previously described (15–21).

**Statistical analysis**

Results are expressed either as single data or as mean  $\pm$  standard error of the mean (SEM) for the indicated number of patients. Student’s *t*-test for paired values was used to calculate statistical significance. Statistically significant differences are indicated as follows: \**P* < 0.05 and \*\**P* < 0.01.

**Results**

**Clinical effects of IFN- $\alpha$  treatment**

Our study was designed as a preliminary study to confirm the originally observed clinical efficacy of IFN- $\alpha$  in patients with severe corticosteroid-resistant asthma (13), to describe side effects of such treatment in these patients, and to understand the potential mode of action by studying immune parameters. In the 10 patients who participated in the study (Table 1), treatment with 3 × 10<sup>6</sup> IU/day was associated with dramatic clinical improvements in each patient as assessed by FEV<sub>1</sub>, peak flow measurements, and required systemic corticosteroid dose (Fig. 1 and Table 2).

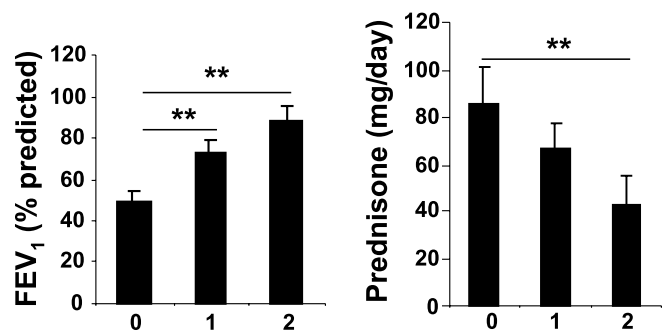


Figure 1. Clinical efficacy of low-dose Interferon (IFN)- $\alpha$  treatment in corticosteroid-resistant asthma. Group mean values (SEM) are presented. 0 = before therapy, 1 = 2–4 weeks IFN- $\alpha$  treatment, 2 = 5–10 months IFN- $\alpha$  treatment. \*\**P* < 0.01.

Table 2. Lung function parameters

Patient	FEV <sub>1</sub> (% pred.)	PEF before BL (l/min)	PEF after BL (l/min)
1	57	180	220
	86	420	460
	103	420	460
2	66	80	100
	91	400	420
	127	nd	nd
3	37	260	280
	65	480	500
	75	380	400
	82	nd	nd
4	37	nd	nd
	48	160	220
	87	460	480
5	84	nd	nd
	26	nd	nd
	31	nd	nd
6	42	nd	nd
	50	140	160
	76	260	300
7	85	320	360
	49	220	260
	67	300	360
8	92	360	400
	69	nd	nd
	93	nd	nd
9	100	nd	nd
	60	200	240
	66	280	350
10	85	180	270
	38	100	180
	70	180	300
	72	170	280

Single results are demonstrated. First line of each patient represents values before treatment. Second line are values after 2–4 weeks and third line after 5–10 months of introducing interferon (IFN)- $\alpha$  treatment. Last two lines in patient 3 demonstrate data at 17 and 18 months of IFN- $\alpha$  treatment. FEV<sub>1</sub>, forced expiratory volume in 1 s; PEF, peak expiratory flow; BL, broncholysis; nd, not determined.

The side effects of IFN- $\alpha$  treatment were largely those expected. We observed a slight increased body temperature in all patients within the first 1–2 weeks of application. Table 3 lists potential side effects of IFN- $\alpha$  and their frequency observed in our study. In patient 3, after 18 months of IFN- $\alpha$ , the treatment was interrupted for a few weeks because of leukopenia. When IFN- $\alpha$  was stopped in this patient, side effects disappeared, but lung function (Table 2) and immunological (see below) parameters also went back to the values observed before treatment. Therefore, the IFN- $\alpha$ -mediated clinical and immunological effects appear to be reversible.

Immunological effects of IFN- $\alpha$  treatment

Numbers of venous blood leukocytes, especially neutrophils, were substantially lowered in all patients given IFN- $\alpha$  (Table 4). Relative numbers of blood lymphocytes

Table 3. Proportion of patients (%) reporting symptoms associated with interferon (IFN)- $\alpha$  treatment

Symptom	2–4 weeks IFN- $\alpha$ (n =10)	5–10 months IFN- $\alpha$ (n =10)
Flue-like symptoms	10 (100)	3 (33)
Headache	5 (50)	5 (50)
Shivering	2 (20)	2 (20)
Tiredness	3 (33)	3 (33)
Lack of appetite	3 (33)	3 (33)
Nausea	9 (90)	5 (50)
Hair loss	0	3 (33)
Depression	0	1 (10)
Amenorrhoe	0	1 (10)
Laboratory findings		
Leukopenia	0	4 (40)
Neutropenia	0	4 (40)
Liver toxicity	2 (20)	2 (20)
Antinuclear antibodies	0	1 (10)
Antibodies against interferon- $\alpha$	0	1 (10)
Thrombocytopenia	0	0
Anemia	0	0

Percentage values are given in parenthesis.

Table 4. Hematological and immunological data

	Before treatment	2–4 weeks IFN- $\alpha$	5–10 months IFN- $\alpha$
Leuko ( $\times 10^9/l$ )	10630 (897)	5568 (503)**	5463 (718)**
Ly (%)	20.8 (3.6)	31.4 (4.7)**	27.3 (3.3)
Mo (%)	6.1 (0.6)	8.8 (0.9)**	7.3 (0.5)**
Neutro (%)	70.7 (4.7)	58.6 (5.3)**	63.3 (3.1)
Eos (%)	2.4 (1.3)	1.2 (0.7)	2.1 (1.1)
CD3 <sup>+</sup> (%)	69.1 (3.6)	76.0 (2.6)*	78.9 (2.3)
CD3 <sup>+</sup> CD4 <sup>+</sup> (%)	44.2 (2.8)	50.2 (2.6)**	53.4 (3.5)*
CD4 <sup>+</sup> CD95 <sup>+</sup> (%)	16.4 (1.9)	18.9 (2.8)	26.7 (3.4)*
CD3 <sup>+</sup> CD8 <sup>+</sup> (%)	25.9 (1.7)	26.2 (1.5)	25.2 (2.8)
CD3/CD4 ratio	1.77 (0.16)	1.99 (0.17)*	2.45 (0.33)*
CD3 <sup>+</sup> CD16 <sup>+</sup> (%)	14.8 (3.2)	12.3 (2.5)	16.5 (9.7)
CD19 <sup>+</sup> (%)	13.2 (3.2)	9.43 (2.7)	10.0 (2.0)
CD14 <sup>+</sup> HLA-DR <sup>+</sup> (%)	83.9 (5.5)	93.3 (2.6)	91.1 (4.9)
SI-PHA	57.5 (15.8)	49.0 (14.6)	86.2 (17.6)

Values are expressed as mean (SEM).

\*  $P < 0.05$ , \*\*  $P < 0.01$  for paired comparison with pretreatment value (Student's  $t$ -test).

were higher upon introduction of cytokine treatment. This was likely due to a relative increase of CD4<sup>+</sup> T cells that also resulted in an increase of the CD4/CD8 ratio. Moreover, CD4<sup>+</sup> T cells expressed higher levels of CD95 (Apo-1, Fas), in particular after several months of IFN- $\alpha$  treatment (Table 4). Increases in relative numbers of monocytes were also associated with IFN- $\alpha$  treatment. Interestingly, IFN- $\alpha$  treatment appeared to increase monocytic HLA-DR expression (CD14<sup>+</sup> HLA-DR<sup>+</sup>), in particular in those patients who presented corticosteroid-mediated decreased levels (Fig. 2). Relative numbers of eosinophils were low in the majority of patients before cytokine therapy (Table 1). In those three patients with elevated eosinophil numbers, IFN- $\alpha$  treatment was

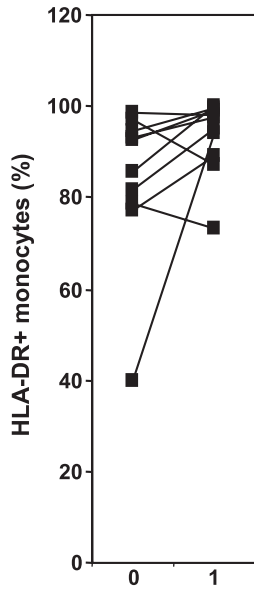


Figure 2. The HLA-DR antigen expression by monocytes from patients with corticosteroid-resistant asthma before and after a 2–4-week treatment with IFN- $\alpha$ . 0 = before therapy, 1 = 2–4 weeks IFN- $\alpha$  treatment. Single results are presented.

followed with a clear reduction of relative and absolute eosinophil numbers. Such anti-eosinophil activity of IFN- $\alpha$  is not obvious when the whole group of patients is considered (Table 4). Relative numbers of natural killer (NK; CD3<sup>-</sup> CD16<sup>+</sup>) and B cells (CD19<sup>+</sup>) did not appear to change during IFN- $\alpha$  treatment.

In an attempt to understand, at least partially, the potential mode of action of IFN- $\alpha$ , we measured cytokine levels upon pan-T cell stimulation with phytohemagglutinine (PHA) and anti-CD3 monoclonal antibody (data not shown) *in vitro*. As it is likely that corticosteroids also influence cytokine levels, prednisone doses were kept constant and measurements were compared between before and after IFN- $\alpha$  treatment. As shown in Fig. 3, IFN- $\alpha$  treatment was associated with significant increases in IFN- $\gamma$  and interleukin (IL)-10 levels. These effects were not associated with increased proliferation rates [see stimulation index (SI-PHA) in Table 4]. In contrast, the classical Th2 cytokines IL-5 and IL-13, which are believed to be heavily involved in asthma pathogenesis (1), remained unchanged. Interestingly, IL-10 expression also increased in *ex vivo* purified T cells and monocytes as a consequence of IFN- $\alpha$  treatment without *in vitro* stimulation (data not shown).

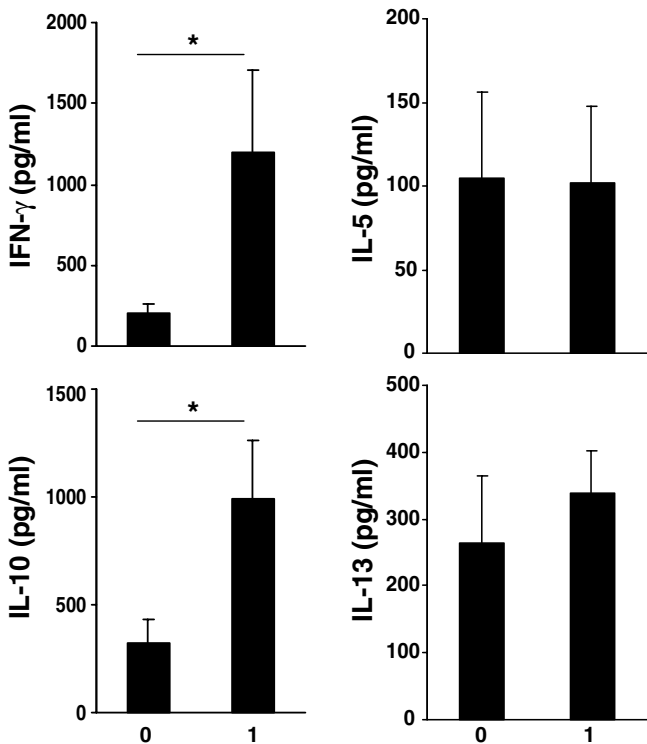


Figure 3. Cytokine production by peripheral blood mononuclear cells following 24-h pan-T cell stimulation with phytohemagglutinine stimulation *in vitro*. Group mean values (SEM) are presented. 0 = before therapy, 1 = 2–4 weeks IFN- $\alpha$  treatment. \* $P < 0.05$ . Same results were observed upon anti-CD3 antibody stimulation (data not shown).

**Discussion**

This trial has shown that IFN- $\alpha$  treatment has high efficacy in patients with severe corticosteroid unresponsive asthma and Churg–Strauss syndrome. Because of the relative corticosteroid resistance, many of our patients had received alternative immunosuppressive drugs such as methotrexate (22) and/or cyclosporine A (23) without a beneficial clinical response before IFN- $\alpha$  treatment. Thus, it appears that IFN- $\alpha$  represents a major breakthrough in the treatment of severe corticosteroid-resistant asthma and fills a previously existing gap of treatment modalities for these asthmatic patients.

The clinical improvement of IFN- $\alpha$  treatment occurred rapidly. Within 1–2 weeks after introduction of the cytokine therapy, lung function parameters dramatically improved, associated with greater physical activity of the patients. Improvements regarding nocturnal asthma and morning dip were also observed. Treatment with IFN- $\alpha$  did not cure asthma, as all clinical and immunological effects were reversible after cytokine withdrawal (patient 3, data not shown). Therefore, a life-long IFN- $\alpha$  treatment appears to be required in severe corticosteroid-resistant asthma, at least until no better drug is available for this group of patients. Because of the rapid clinical improvement, the corticosteroid dose of the first three patients was already decreased within 2–4 weeks upon introduction of IFN- $\alpha$  therapy. In patients 4–10, in which IFN- $\alpha$  also rapidly improved the clinical situation, the given amount of prednisone was kept constant to avoid the possibility that any observed immunological effect

might be the consequence of a reduced corticosteroid dose.

As demonstrated in earlier studies, IFN- $\alpha$  also had side effects. The most frequent problems associated with early IFN- $\alpha$  therapy were flue-like symptoms, nausea, and headache. The frequency of the first two mentioned symptoms decreased after several months of treatment. Increased levels of liver enzymes were observed in 20% of the treated patients. In one patient, anti-IFN- $\alpha$  antibodies were found after 6 months of treatment. In case of serious side effects, reduction of the IFN- $\alpha$  dose appears to reduce side effects without losing efficacy (patient 5). The side effects of IFN- $\alpha$  should be taken into consideration and the potential benefit/risk ratio calculated before starting the cytokine therapy.

Asthma has been considered as an allergic disease associated with increased Th2 activity (1). Therefore, analyzing the pathologic immune response may provide clues for the therapeutic efficacy of IFN- $\alpha$ . This is the first published clinical study with IFN- $\alpha$  in which a quantitative analysis of lymphocyte subpopulations is reported. The relative increase of CD4<sup>+</sup> T cells was a consistent finding, although, after breaking corticosteroid resistance, corticosteroids may overcome this effect and CD4<sup>+</sup> T cell numbers can also decline. The IFN- $\alpha$  treatment dramatically increased the capacity of peripheral blood T cells to generate IFN- $\gamma$ , suggesting that Th1 differentiation was positively influenced by the cytokine therapy. This is in agreement with a previous report demonstrating that allergen-specific T cell clones generated in the presence of IFN- $\alpha$  produced Th1 but not Th2 cytokines (12). Our study provides evidence for IFN- $\alpha$ -mediated increased Th1 activity *in vivo*, as markedly increased HLA-DR expression on monocytes [this marker mostly depends on gene expression of IFN- $\gamma$  (14)] was observed in response to IFN- $\alpha$  in those patients with deficient monocytic HLA-DR expression before treatment. How IFN- $\alpha$  preferentially favors Th1 differentiation remains unclear, but previously published work performed *in vitro* suggested that it activates signal transducer and activator of transcription 4 (STAT4), a transcription factor required for Th1 cytokine expression (24). The establishment of a correct Th1/Th2 balance may improve defense mechanisms against infectious pathogens. On the contrary, IFN- $\alpha$  has also direct anti-viral effects, and, perhaps, many of our severe asthmatic patients suffered from an underlying persistent viral disease (25).

Interleukin-10 is considered as being an anti-inflammatory cytokine predominantly produced by monocytes and T cells (26). Corticosteroids mediate their anti-inflammatory effects at least partially by inducing the IL-10 gene (27). Moreover, it has recently been observed that patients with corticosteroid-resistant asthma have a defect in corticosteroid-induced IL-10 production (28). From this point of view, increased expression of IL-10 in venous blood T cells and monocytes as a consequence of IFN- $\alpha$  treatment is an interesting finding, as it further

supports the hypothesis that IFN- $\alpha$  broke the corticosteroid resistance in our group of patients. On the contrary, IFN- $\alpha$  has been shown to directly stimulate IL-10 gene production in CD4<sup>+</sup> T cells and monocytes *in vitro* (29). Regardless from the exact molecular details, IFN- $\alpha$  might enhance the negative feedback mechanism ascribed to IL-10, which limits the inflammatory asthmatic reaction. First long-term investigations on cytokine levels suggest that the rapid immunological changes described in this article are maintained as long as IFN- $\alpha$  is given to the patient (data not shown). Besides IL-10, IFN- $\alpha$  has also been described as a putative cytokine able to induce the expression of the immunosuppressive IL-1 receptor antagonist (30). In conclusion, there is increasing evidence that the original picture of IFN- $\alpha$  as a pro-inflammatory cytokine is an oversimplification and should be reconsidered.

Eosinophils are considered as major effector cells in asthma (31). Many of the patients investigated in this study had very low numbers of eosinophils in spite of the severe clinical condition. Therefore, although IFN- $\alpha$  treatment clearly reduced eosinophil numbers in those patients who presented eosinophilia, the clinical effect seen in all 10 investigated patients cannot be explained by the potential anti-eosinophil activity of IFN- $\alpha$ . Furthermore, although eosinophils express a receptor for IFN- $\alpha$  (32), this study provides evidence that eosinophil numbers are largely regulated by the bioactivity of corticosteroids. For instance, in some patients, we observed an increase in eosinophil numbers in spite of IFN- $\alpha$  treatment, probably because of reduction of the corticosteroid dose. This observation points to a potential risk associated with IFN- $\alpha$  treatment: rapid or exaggerated reduction of the corticosteroid dose may indirectly provoke eosinophilic inflammation and consequently deteriorate the asthma. In contrast, if the corticosteroid dose is not sufficiently reduced, patients may develop a severe corticosteroid-induced immunosuppression (15). Therefore, careful immunomonitoring is recommended until the patients are in a stable clinical situation. In spite of the difficulties in handling, IFN- $\alpha$  is the first therapeutic option in corticosteroid-resistant asthma that is indeed clinically effective in each patient. Future clinical studies, perhaps with a depot preparation of IFN- $\alpha$  (7), will provide further insight into the mechanism(s) responsible for its clinical efficacy.

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