

## Determinants of response to immunosuppressive therapy in idiopathic pulmonary fibrosis

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**ABSTRACT:** Idiopathic pulmonary fibrosis (IPF) response to corticosteroids and cytotoxic medications appears to be the most important determinant of survival. The purpose of this retrospective study was to analyse the determinants of response to immunosuppressive therapy with prednisone alone, or prednisone and cyclophosphamide, in IPF.

Twenty five consecutive patients were studied. Initial evaluation in untreated patients included clinical, biological and functional parameters. Sequential evaluation by pulmonary function tests (forced vital capacity (FVC) and transfer factor of the lungs for carbon monoxide (TLCO)) was performed at a 3 month interval. Response to therapy was defined as an improvement in FVC and/or TLCO of more than 10% after 12 months, with maintenance of this improvement for at least another 12 months. Twelve of the 25 patients were classified as responders.

A symptomatic disease of less than 12 months duration before onset of therapy related to response. FVC was more impaired in the group of responders when the comparison was limited to patients with an FVC of less than 90%. Bronchoalveolar lavage cell counts were not significantly different between responders and non-responders. Assessment of pulmonary function after 3 months of treatment was predictive of maintenance of the response or of even further improvement. Patients with improved FVC after 3 months of therapy had a significantly shorter symptomatic disease before onset of treatment ( $7.6 \pm 7.1$  vs  $20.2 \pm 18.6$  months). A beneficial effect of addition of cyclophosphamide was observed only in patients who demonstrated an early but short-lived improvement to steroids. Adverse reactions of immunosuppressive therapy were noticed in 10 patients, and required discontinuation of treatment in six of them. Morbidity from cyclophosphamide toxicity was evident in six patients, whilst five of them failed to demonstrate response to cyclophosphamide.

In conclusion, our retrospective study suggests that patients with a shorter symptomatic period prior to initiating treatment are more likely to respond to treatment. Early assessment of changes in FVC in individual patients may provide information regarding the likelihood of response to treatment. Early but short-lived corticosteroid effects may be reverted to sustained therapeutic effects by the addition of cyclophosphamide.

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Idiopathic pulmonary fibrosis (IPF) is a severe inflammatory disorder with an almost invariably poor prognosis, and a median survival ranging 4–6 years [1–6]. Major problems in management result from the variable rate of disease progression and the difficulties in predicting response to therapy. Results of therapy with corticosteroids are poor since few patients experience improvement or at least stabilization of the disease process [3–7]. As response to therapy proved to be the primary determinant of prognosis and prolonged survival [2–4, 8], other treatment regimens combining low dose

corticosteroids with immunosuppressive agents have been investigated. Substantial variability in response to regimens including azathioprine, cyclophosphamide or D-penicillamine has been demonstrated in uncontrolled studies [7–10]. This can be explained by the different dosage regimens and by the variability of criteria used for assessing the response to therapy, some studies requiring sustained improvement of pulmonary function tests, others relying mainly on subjective and radiological changes. Randomized, controlled trials comparing prednisone and cyclophosphamide and/or azathioprine with

prednisone alone reported a trend towards better survival that was not significant. Furthermore, these regimens cannot prevent deterioration in a majority of patients [11–17]. These findings raised concern regarding prolonged use of cytotoxic agents, because of the risk of severe side-effects which may result in further clinical deterioration [3, 16]. Therefore, attempts have been made to identify patients that are more likely to respond to therapy. Pretreatment variables associated with responsiveness include a shorter duration of symptoms, female sex, a high cellularity with less fibrosis on biopsy specimens, and a high lymphocyte count in bronchoalveolar lavage fluid [2, 8, 18–21].

Furthermore, it seems important to know whether early clinical assessment of response can predict ultimate outcome and reduce unnecessary long-term exposure of therapy-resistant patients to agents with potentially hazardous side-effects. There is evidence that patients responding to corticosteroids experience most of their improvement within three months, whereas response to adjuvant immunosuppressive agents seldom becomes obvious before one year of treatment [8–11]. WATTERS *et al.* [18] demonstrated that, in patients treated with corticosteroids, the clinical outcome at 6 months was related to outcome at 12 months. However, data regarding relationship between early outcome and long-term response are lacking.

This retrospective study reports on 25 consecutive patients with IPF who were treated with corticosteroids, either alone or in combination with cyclophosphamide. The purpose of this study was to identify variables prior to onset of treatment that were associated with response to therapy. We further evaluated the effect of cyclophosphamide on the progression of disease. In addition, we examined the usefulness of early assessment of improvement in predicting sustained response to treatment.

## Patients and methods

### Study population

Twenty five consecutive patients (8 females and 17 males, mean age  $48 \pm 15$  yrs, 10 smokers and 15 non-smokers) presenting with IPF were included in this retrospective study. Diagnosis of IPF was based on the presence of progressive breathlessness, bilateral dry crackles, finger clubbing, widespread bilateral shadowing on chest roentgenogram, and pulmonary function tests showing either a reduced total lung capacity (TLC), reduced forced vital capacity (FVC), decreased single-breath carbon monoxide transfer factor (TLCO), resting hypoxaemia or exercise-induced hypoxaemia. The duration of respiratory symptoms before the start of treatment was taken as the duration of the disease. Patients with a collagen-vascular disorder or with a clinical history of environmental exposure, hypersensitivity pneumonitis, drug-induced pulmonary disease or chronic pulmonary infection were excluded. Histological confirmation of the diagnosis was obtained before treatment in all patients.

Twenty one patients had open lung biopsy (OLB), and transbronchial biopsy (TBB) was performed in four patients, who had fulfilled all clinical and radiological criteria and who presented with pulmonary function tests showing reduced lung volumes or decreased TLCO. All biopsy specimens showed varying degrees of interstitial fibrosis. Interstitial and alveolar cellular infiltration were present in most, consisting of macrophages, lymphocytes, neutrophils and occasionally eosinophils or histiocytes. None had evidence of granuloma, significant inorganic material by polarized light microscopy, infection or malignancy.

Serological studies were performed in all patients, including tests for antinuclear antibody (ANA), rheumatoid factor and serum protein electrophoresis. The serum was tested for the presence of precipitating antibodies to *Aspergillus* species, *Thermoactinomyces vulgaris*, *Micropolyspora faeni* and pigeon products (Ouchterlony gel diffusion techniques). Complement factors 3 and 4 were also measured.

### Treatment regimens and follow-up

Treatment was started in all patients after initial evaluation. Oral prednisone was given at an initial dose of  $1 \text{ mg} \cdot \text{kg}^{-1}$  ( $51.1 \pm 14 \text{ mg} \cdot \text{day}^{-1}$ ). After onset of therapy, patients were seen at the hospital at 3 monthly intervals. Each follow-up evaluation included detailed history of pulmonary symptoms and breathlessness, physical examination, posteroanterior and lateral chest roentgenogram, and pulmonary function tests. Special attention was paid to adverse reactions to therapy. In patients receiving cyclophosphamide, blood cell counts were performed at two weekly intervals. Patients who demonstrated clinical, radiological and physiological evidence of improvement with prednisone had their dose tapered to 20–40 mg daily. Patients who did not improve were treated with cyclophosphamide (100 mg daily) together with prednisone (mean dose  $0.5 \text{ mg} \cdot \text{kg}^{-1}$  daily).

### Response to treatment

Response was defined as a measurable change in lung function at the 12 month assessment, that was sustained for at least another 12 months. Patients were classified as responders if pulmonary function tests demonstrated improvement from baseline in FVC and/or TLCO of more than 10% 12 months and 24 months after onset of therapy. Patients failing to meet these criteria were considered as nonresponders.

### Pulmonary function tests

(FVC) and forced expiratory volume in one second ( $\text{FEV}_1$ ) were determined using a Jaeger spirometer. TLCO was obtained by the single-breath method and corrected for haemoglobin. The predicted values for each subject, based on sex, age and height, were obtained from standard tables [22]. Data were expressed as percentages of the predicted values.

*Bronchoalveolar lavage*

Bronchoalveolar lavage (BAL) was performed after premedication with atropine under local anaesthesia with lignocaine, using a wedged fiberoptic bronchoscope (Model BF B<sub>3</sub>; Olympus Corp. of America, New Hyde Park, NY, USA) and 250 ml of sterile saline solution in aliquots of 5×50 ml, with immediate gentle vacuum aspiration after each aliquot [23]. The aspirated fluid was collected into sterile siliconized jugs and immediately transported on ice to the laboratory. The total volume of recovered fluid was noted. The cells were separated from the lavage fluid by low speed centrifugation (800×g for 10 min). The cells were resuspended in Hank's solution and evaluated for total number and differential cell count. Total cell count was expressed as the total number of cells per millilitre of recovered fluid.

*Statistical analysis*

All data are expressed as mean±SEM unless otherwise stated. Comparison of means in groups was made by Wilcoxon's rank sum test (nonparametric data). Four-fold table comparisons were performed by Chi-squared test or Fisher's exact test.

**Results**

The clinical and physiological characteristics of each individual patient prior to onset of treatment are displayed in table 1. After a 24 month follow-up, 12 patients (Nos. 1–12) were considered as responders. Three of these had a sustained improvement in FVC as well as in TLCO; an isolated increase in FVC was demonstrated in six (TLCO was not measured in 2); and three patients

Table 1. Characteristics of 25 patients with idiopathic pulmonary fibrosis

Pat No.	Sex	Age at start of treatment	Smoking	Duration of symptoms prior to treatment	Pre-treatment pulmonary function			Treatment	Follow-up since onset of treatment	Survival
		yrs	pack-yrs	months	FVC % pred	TLCO % pred	Pao <sub>2</sub> kPa		months	
<b>Responders (n=12)</b>										
1	M	50	0	36	92	69	11.5	P	65	Alive
2	F	33	0	2	44	73	8.8	P/P+C	26	Alive
3	M	54	0	8	80	61	9.6	P/P+C	34	Alive
4	M	40	0	3	61	55	11.3	P/P+C	57	Alive
5	M	69	25	22	41	ND	9.1	P	38	Alive
6	M	46	24	8	52	48	11.3	P/P+C	28	Alive
7	M	37	0	60	60	32	9.9	P/P+C	95	LT
8	F	56	0	15	65	128	10.4	P/P+C	40	Alive
9	F	53	0	6	61	55	9.2	P	104	Died
10	M	67	40	4	48	ND	6.7	P	45	Alive
11	M	47	25	6	93	76	8.4	P	42	Alive
12	F	19	0	3	62	31	11.1	P	38	Alive
Mean		48	9.5	14.4	63	63	9.8		51	
SEM		3	4.2	5	5	8	0.4		7.2	
<b>Nonresponders (n=13)</b>										
13	M	47	20	60	79	44	10.7	P+C	28	Died
14	F	39	0	36	70	52	11.1	P+C	34	Alive
15	F	56	0	12	106	74	7.1	P/P+C	105	Alive
16	M	28	5	12	108	28	7.9	P/P+C	124	Died
17	M	71	70	24	108	41	9.6	P/P+C	30	Died
18	M	45	0	12	57	61	9.3	P/P+C	67	Died
19	M	18	0	12	59	ND	6.5	P	36	Alive
20	M	59	0	20	79	57	11.2	P/P+C	42	Died
21	F	38	0	3	62	38	9.9	P/P+C	32	LT
22	M	67	10	12	75	57	10.4	P	34	Alive
23	M	59	30	3	89	107	9.5	P+C	46	LT
24	M	68	27	16	68	39	10.7	P/P+C	34	Alive
15	F	45	0	60	54	56	10.0	P/P+C	28	Alive
Mean		49	12.5	21.7	78	55	9.5		49.2	
SEM		5	5.8	5.4	6	6	0.4		8.8	

Pat: patient; M: male; F: female; P: prednisone; P+C: prednisone+cyclophosphamide; P/P+C: switch from prednisone to prednisone+cyclophosphamide; FVC: forced vital capacity; TLCO: single-breath diffusing capacity of the lungs for carbon monoxide; Pao<sub>2</sub>: arterial oxygen tension; ND: not determined; LT: lung transplant.

had an increase in TLCO without concomitant improvement in FVC. Thirteen patients were classified as nonresponders. Two of these demonstrated initial improvement in FVC and/or TLCO of more than 10% which was not sustained at 24 months. Eleven patients failed to show any improvement in FVC at 12 and 24 months.

#### Treatment regimens

Six patients in the responder group were treated with prednisone alone. Six were treated first with prednisone and then after 6 or 9 months ( $7 \pm 1.4$  months), with cyclophosphamide together with prednisone, because they did not demonstrate significant sustained improvement with prednisone alone. In the group of nonresponders, two patients (Nos 19 and 22) received prednisone alone during their follow-up of 24 months. Both had demonstrated improvement of breathlessness and an increase in lung volumes at the 6 and 12 month assessment, but were deteriorating at 24 months. Eight patients had their therapy changed from prednisone alone to prednisone and cyclophosphamide, since they failed to demonstrate improvement after a 3 month therapy with prednisone alone. Three patients receive prednisone and cyclophosphamide immediately, because of advanced disease in two cases (severe dyspnoea with widespread honeycombing on computed tomographic CT scan in Nos 13 and 23), and a lack of benefit of an earlier treatment with prednisone in the third case (No. 14).

#### Clinical, physiological and biological findings in responders and nonresponders

There was no significant difference between responders and nonresponders in age ( $48 \pm 3$  vs  $49 \pm 5$  yrs), or in smoking habits (4/12 responders were smokers vs 6/13 nonresponders). Response rate was similar between female patients (50%) and males (47%). Responders tended to have a shorter duration of symptoms prior to onset of treatment than nonresponders, but the difference did not reach significance ( $14.4 \pm 5$  vs  $21.7 \pm 5.4$  months). However, a symptomatic disease of less than 12 months before onset of treatment appeared to be useful in predicting good response to therapy: 8/10 patients with symptomatic disease of less than one year duration responded to therapy, whilst only 4/15 patients with longer symptomatic disease were responders ( $p < 0.05$ , Fisher's exact test).

The evolution of pulmonary function parameters of responders and nonresponders from baseline (prior to onset of treatment) to 24 months follow-up is shown in figure 1. The improvement in FVC at 12 and 24 months in responders was statistically significant ( $p = 0.001$  and  $p = 0.002$ , respectively) whereas TLCO did not significantly change.

We observed a trend towards a lower initial FVC in responders ( $63.2 \pm 4.9\%$  vs  $78 \pm 5.5\%$  predicted;  $p = \text{NS}$ ).

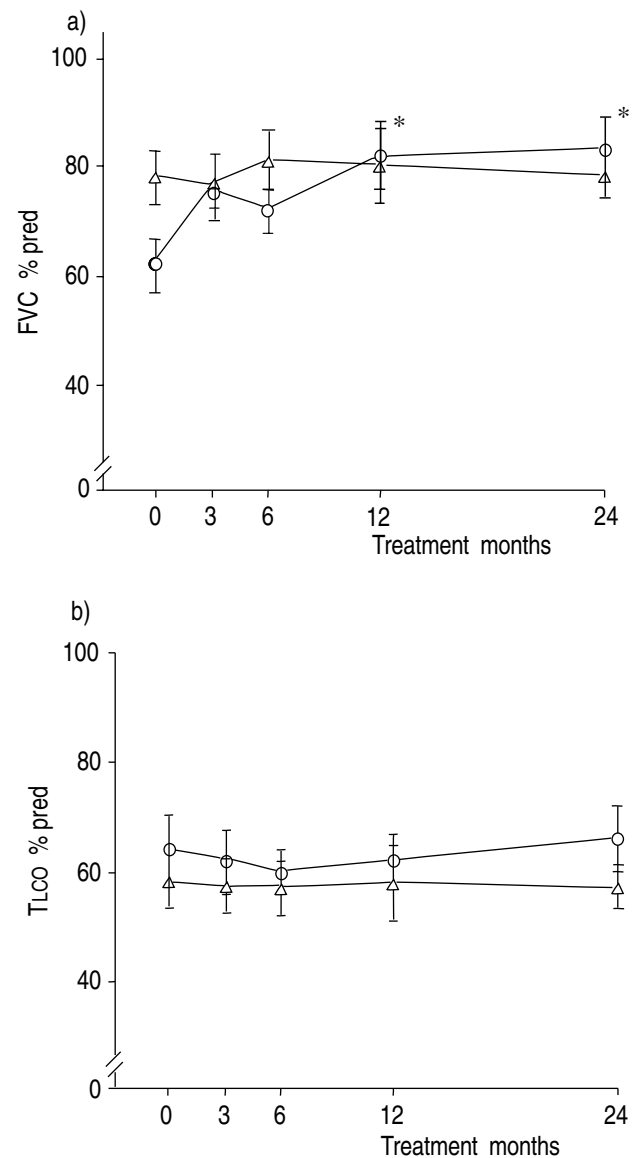


Fig. 1. — Comparison of pulmonary function variables: a) FVC; b) TLCO, before and after 3, 6, 12 and 24 months of follow-up. —○—: responders (n=12); —△—: nonresponders (n=13). \*: significantly different from values at 0 month in the group of responders. FVC: forced vital capacity; TLCO: transfer factor of the lungs for carbon monoxide.

However, five patients showed a FVC of greater than 90% predicted (range 92–108% pred) prior to onset of treatment (table 1). As one could argue that FVC was not impaired in these patients, and response by means of increasing FVC was, therefore, unlikely to occur, we limited the comparison to patients with an initial FVC of less than 90% of predicted values. The responders still had a lower FVC than the nonresponders and the difference was significant ( $57.4 \pm 3.1$  vs  $69.2 \pm 3.1\%$ ;  $p = 0.04$ ). There was no difference in TLCO and resting arterial oxygen tension ( $P_{aO_2}$ ) between the two groups of patients. The initial lung lavage cellular contents in responders and nonresponders are shown in table 2: none of the differences achieved statistical significance.

Table 2. – Bronchoalveolar lavage differential cell count in the study population

	Responders	Nonresponders
Total cells·ml <sup>-1</sup> ×10 <sup>-3</sup>	296±152	342±292
Alveolar macrophages		
%	70±21	69.8±24
cells·ml <sup>-1</sup> ×10 <sup>-3</sup>	192±104	216±204
Lymphocytes		
%	15±13.9	14.3±11.9
cells·ml <sup>-1</sup> ×10 <sup>-3</sup>	46.8±72	34.4±32
Neutrophils		
%	13.4±19	14.1±26
cells·ml <sup>-1</sup> ×10 <sup>-3</sup>	39.9±76	84±147
Eosinophils		
%	2.1±2.4	1.7±2.7
cells·ml <sup>-1</sup> ×10 <sup>-3</sup>	4.8±4.7	2.3±4.1

All data are presented as mean±SEM.

#### Early clinical assessment of improvement and ultimate response to therapy

To identify pretreatment variables that were related to response to therapy, we determined whether early outcome, assessed by easily available pulmonary function measurements, such as FVC, had a predictive value in determining ultimate response to treatment. As a criterion for early improvement, we used an increase in FVC of more than 10% from baseline after 3 months of therapy. Measurements of TLCO were not included, because data were missing in five patients. Early assessment of individual patients was important in showing a significant correlation between an improvement in FVC of more than 10% at 3 months and subsequent response to therapy. Eight out of 9 patients with early improvement of FVC responded to treatment, whereas 10/16 patients without early improvement in FVC did not respond ( $p=0.03$ ).

Age, sex, smoking habits, pulmonary function tests and BAL differential cell counts at baseline were not different between patients with early improvement and patients without improvement. However, the duration of symptoms prior to onset of treatment was significantly shorter in patients who experienced early response ( $7.6 \pm 7.1$  vs  $20.2 \pm 18.6$  months;  $p < 0.05$ ).

#### Progression of disease and survival

Eleven out of 12 responders were alive at the time of the report. Three patients were still treated with prednisone (Nos 1, 5 and 10). All treatment was stopped in six patients (Nos 3, 4, 6, 8, 11 and 12). Cyclophosphamide was withdrawn and prednisone continued alone in one patient (No. 2). One patient (No. 7) started to deteriorate slowly after 5 yrs of therapy and lung transplantation was performed 3 years later. One death occurred in the group of responders.

Eight out of 13 nonresponders were alive at the time of the report. All treatment was stopped in three. Three received steroids, one prednisone and cyclophosphamide, and lung transplant was performed in one. Five

deaths occurred: four patients died of respiratory failure due to progression of IPF, and one of pulmonary embolism.

#### Influence of cyclophosphamide on progression of disease

In order to assess the benefit of cyclophosphamide, we evaluated pretreatment variables and the changes in FVC and TLCO in the 14 patients (6 responders and 8 non-responders) whose therapy with prednisone alone (P) was changed for a regimen combining cyclophosphamide with prednisone (P+C). Age, sex, smoking habits, pulmonary function tests and BAL cell counts at baseline were not different between these patients. Figure 2 illustrates percentage changes from baseline in FVC and TLCO that were obtained with prednisone alone and the subsequent evolution during treatment with

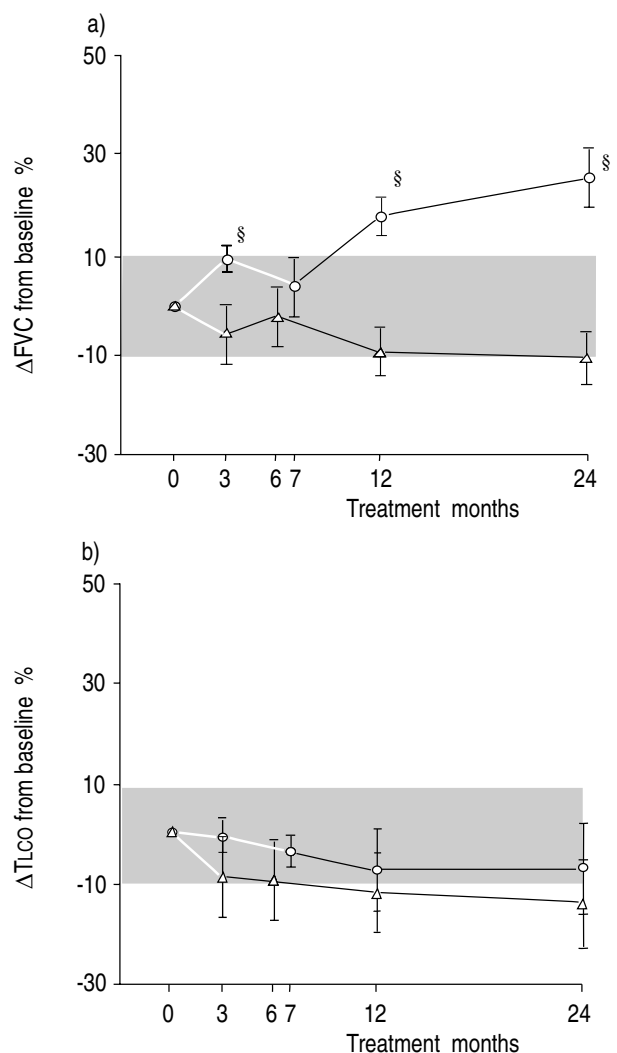


Fig. 2. – Change in a) FVC and b) DLCO obtained during treatment with prednisone alone (white lines) and subsequent treatment with cyclophosphamide in combination with low dose of prednisone (black lines). Values are expressed as percentage change from baseline. A change in FVC or TLCO of less than 10% in either direction signified stability (represented by the shaded area). —○—: responders (n=6); —△—: nonresponders (n=8); §: significantly different from non-responders.

Table 3. – Adverse effects of treatment

Adverse effects	Pat No.	Treatment				Modification of treatment regimen
		Prednisone months	mg*	Cyclophosphamide months	mg*	
<b>Infection</b>						
<i>Mycobacterium kansasii</i>	3	15	37	12	100	Discontinuation of all treatment
Cryptococcal meningitis	16	58	47	42	100	Tapering of prednisone/discontinuation of cyclophosphamide
Bacterial bronchopneumonia	15	4	60	2	100	Tapering of prednisone
	19	6	0	-	-	None
<b>Haematotoxicity</b>						
Anaemia and leucopenia	15	18	35	15	100	Discontinuation of cyclophosphamide
Lymphopenia	20	28	42	22	100	Discontinuation of cyclophosphamide
Minor haematuria	7	78	50	72	150	None
	16	70	45	6	50	None
Haemorrhagic cystitis	16	105	30	39	50	Discontinuation of cyclophosphamide
	23	-	-	42	100	Discontinuation of cyclophosphamide
Disabling osteoporosis	22	13	70	-	-	Tapering of prednisone
Aseptic bone necrosis	19	32	70	-	-	Tapering of prednisone
Gastrointestinal bleeding (ulcer)	20	42	41	-	-	None
Weight loss	21	24	25	9	100	Discontinuation of cyclophosphamide

\*: mean daily dose.

cyclophosphamide and prednisone (P+C). Early assessment of FVC (3 months) demonstrated that responders to P+C demonstrated a significant early improvement to steroids, which was not sustained and implied subsequent addition of cyclophosphamide. Addition of cyclophosphamide did not significantly modify TLCO.

#### Adverse effects

A total of 14 adverse effects were observed in 10/25 patients (40%) during immunosuppressive therapy (table 3). Four patients suffered complications that were due to prednisone and could be controlled with symptomatic therapy and dose reduction of corticosteroids. Adverse effects were significantly more frequent in nonresponders (8/13) than in responders (2/12).

Among the 17 patients treated with cyclophosphamide and prednisone, six patients developed a total of 10 adverse effects. Evidence of specific cyclophosphamide toxicity was seen in six patients (7 adverse reactions), between 9 and 105 months after starting treatment. Haematological toxicity with anaemia and reduced neutrophil count or lymphocyte count was seen in two patients, and transient minor haematuria in another two. Haemorrhagic cystitis developed in two patients; and one had weight loss that coincided with the onset of cyclophosphamide treatment. Furthermore, severe infectious complications were observed in three patients whilst they received cyclophosphamide and prednisone. Cyclophosphamide was discontinued in six patients because of adverse reactions. In one patient (No. 16) cyclophosphamide was first stopped after he had developed a cryptococcal meningitis. Therapy was

reinstated 10 months later, but was irrevocably discontinued when he developed haemorrhagic cystitis.

#### Discussion

The present study suggests that early assessment of changes in FVC in individual patients with IPF may provide information regarding the likelihood of response to treatment, and that early but short-lived corticosteroid effects may be reverted to sustained therapeutic effects by the addition of cyclophosphamide.

We defined response to therapy as a sustained (>24 months) improvement in pulmonary function testing. The clinical relevance of changes in FVC for the evaluation of response to immunosuppressive treatment in IPF has been demonstrated previously [21]. However, FVC may not be sensitive enough, since a subset of patients with IPF have normal lung volumes [1]. Therefore, an alternative criterion was introduced, *i.e.* sustained improvement (>24 months) in TLCO. We think that the three patients who fulfilled the second criterion were correctly considered as responders, because they also demonstrated improvement in exercise tolerance and regression of pulmonary infiltrates on chest roentgenogram. Furthermore, their improvement in TLCO was sustained during follow-up ranging 42–65 months.

In our study, several features seem to be related to clinical response. Firstly, a symptomatic disease of less than 12 months before onset of treatment as already reported [8, 21]. This may reflect different stages of the disease and/or efficacy of treatment in the earliest stages of IPF. Accordingly, SCHWARTZ *et al.* [24] reported that several clinical characteristics were associated with

further deterioration of pulmonary function tests in IPF, including smoking habits and dyspnoea. This latter suggests that patients with less lung involvement appear to have a more benign course. Secondly, among the pretreatment lung function tests, initial values of FVC were found to be lower in responders than in nonresponders. A lower pretreatment FVC in responding patients was also noted by RUDD *et al.* [21]. Thirdly, there was a significant correlation between early improvement of FVC and response to therapy at 24 months. This is consistent with the findings of WATTERS *et al.* [18], who showed, in a series of 26 patients with newly diagnosed IPF, that the trend in clinical course established after 6 months of therapy with corticosteroids persisted at the 12 month evaluation.

Other parameters, such as BAL or gallium-67 scanning, will possibly prove their usefulness as prognostic tools [19]. For example, some studies have reported isolated increases in eosinophils and/or neutrophils in pretreatment BAL of patients who fail to respond to immunosuppressive drugs [14, 20, 25]. However, selected patient groups were small and the inclusion of patients with collagen vascular-associated interstitial lung disease distorts interpretation. In addition, different standardization of BAL procedures and effects of previous therapy or smoking habits can be an additional cause of variability. Clearly, prediction of disease progression might help to select patients who need potentially toxic treatment [26]. AGUSTI *et al.* [27] recently suggested that both the single-breath CO transfer factor and exercise testing (alveolar to arterial oxygen tension difference ( $\Delta A-a P_{O_2}$ )) could be useful prognostic indicators of the decline of arterial oxygenation over time in IPF. We did not find such a correlation, but it should be pointed that no patient received immunosuppressive drugs throughout the period of the latter study, whereas our results suggest that early but short-lived corticosteroid effects may be reverted to sustained therapeutic effects by the addition of cyclophosphamide.

Results of therapeutic interventions in patients with IPF remain difficult to interpret, as the natural history of the disease in untreated patients is not fully understood and the rate of disease progression is highly variable [2, 3]. The differences in response rates and in extent of improvement encountered in the literature can be explained by the heterogeneity of study populations and the lack of uniformity in dosage of therapeutic agents and in definition of response. Corticosteroids are generally accepted as the first-line treatment. Clinical improvement is seen in 20% of patients, and this response is also related to improved survival [2–8]. However, long-term efficacy of corticosteroids has not been investigated by controlled trials. Cytotoxic agents, such as cyclophosphamide, are recommended for patients who are resistant to corticosteroids [5–11, 13]. Arguments in favour of its benefit have been suggested mainly in anecdotal reports and in uncontrolled studies with limited numbers of patients [9, 10, 12]. So far, there has only been one randomized controlled trial comparing corticosteroids alone to a combination regimen of cyclophosphamide and corticosteroids in terms

of response rate and survival JOHNSON *et al.* [11] randomized 43 patients to receive either prednisolone alone (60 mg daily for 1 month, then decreasing by 5 mg weekly to a maintenance dose of 20 mg every other day) or low dose prednisolone (20 mg every other day) and cyclophosphamide (100–120 mg daily). However, they also included patients with rheumatoid arthritis, Sjögren's syndrome and polyarthritis with Raynaud's phenomenon. They found no difference in therapeutic response between both treatment regimens, which by the end were considered as equally effective [11]. Much less promising results with cyclophosphamide were obtained by ELIASSON *et al.* [16], who found no evidence of efficacy in eight patients with steroid resistant IPF. There was progressive deterioration during treatment and three patients even experienced increasing dyspnoea.

Although, in our study, the limited number of patients does not allow valid statistical conclusions, temporal sequence of improvement suggests that cyclophosphamide may be useful in patients demonstrating early clinical improvement under steroids and that it has no effect in late stages of IPF. This raises the question of whether cyclophosphamide should be added early on in patients demonstrating clinical improvement after a short-term treatment with corticosteroids. In the same way, one could ask whether it is reasonable to give cyclophosphamide as an additional agent in patients without early improvement under corticosteroids. In this context, early identification of patients with a high probability of resistance to treatment is of interest, as it could avoid unnecessarily long exposure to drugs without positive impact on the patient and with potentially hazardous side-effects. Although clinical deterioration in patients with IPF is most frequently due to disease progression or disease-associated complications, such as infection, heart failure, bronchogenic carcinoma or thromboembolism [17], morbidity due to adverse effects of therapy remains an important issue. An important observation was that cyclophosphamide was responsible for major side-effects in five patients who did not show any response to this medication.

In this context, other potential therapies have been proposed. Because azathioprine appears to be well-tolerated [18], a switch from cyclophosphamide to azathioprine in responders might provide an interesting alternative to minimize intolerable side-effects. A preliminary report also suggests that colchicine might be as effective as, and less toxic than, immunosuppressive therapy since a retrospective study of treatment with colchicine in IPF demonstrated improvement in 22% cases [28]. Lastly, experimental studies support the hypothesis that human recombinant soluble tumour necrosis factor (TNF) receptor might be useful in treatment of pulmonary fibrosis induced by bleomycin or silica in mice [29].

Further randomized controlled studies are needed to more precisely define the subgroups of IPF patients likely to respond to immunosuppressive treatment. These studies should at best assess homogeneous populations and control duration of disease and features of early clinical response.

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