Eur Respir J 1998; 12: 1409–1414
DOI: 10.1183/09031936.98.12061409
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

Cyclophosphamide pulse therapy in idiopathic pulmonary fibrosis

M. Kolb, J. Kirschner, W. Riedel, H. Wirtz, M. Schmidt

Cyclophosphamide pulse therapy in idiopathic pulmonary fibrosis. M. Kolb, J. Kirschner, W. Riedel, H. Wirtz, M. Schmidt. ©ERS Journals Ltd 1998.

ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is a progressive disorder with poor prognosis. Response to treatment is infrequent and the use of immunosuppressive agents other than corticosteroids is the subject of ongoing discussion because of uncertain efficacy and side-effects.

To determine the efficacy and safety of cyclophosphamide pulse therapy in IPF, this study retrospectively analysed 18 patients with progressive IPF who were treated with intermittent *i.v.* cyclophosphamide (1–1.3 g·month^{-1}) and additional oral prednisolone for 1 yr. Static lung volumes, arterial oxygen tension (P_{a,O_2}) at rest, clinical symptoms and potential treatment-related side-effects were recorded.

Cyclophosphamide had to be stopped in one patient, owing to repeated pulmonary infection; 11 patients were responders (five improving, six stabilizing) and six patients deteriorated. The change in vital capacity (VC) of responders was +6.7±18.0% (mean ±SD), compared with -20.6±18.2% in nonresponders (p=0.008). P_{a,O_2} remained constant in responders (+0.13±0.88 kPa (+1.0±6.6 mmHg)), while it decreased in nonresponders (-2.08±1.92 kPa (-15.6±14.4 mmHg, p=0.008)). Additional prednisolone was reduced by 19.1±13.4 mg in responders, compared with 6.7±16.3 mg in nonresponders (p=0.02). VC at initiation of therapy was higher in responders (60.2±10.2 *versus* 40.3±12.9% predicted; p=0.004). No side-effects occurred, other than respiratory tract infection.

These data demonstrate that intravenous cyclophosphamide pulse therapy may be a favourable regimen for certain patients with progressive idiopathic pulmonary fibrosis. Patients with a vital capacity of more than 50% predicted and a shorter duration of disease may benefit most.

Eur Respir J 1998; 12: 1409–1414.

Dept of Medicine, University of Würzburg, Germany.

Correspondence: M. Kolb
Dept of Medicine
University of Würzburg
Josef-Schneider-Str. 2
D-97080 Würzburg
Germany
Fax: 49 9312012254

Keywords: Cyclophosphamide
lung fibrosis
pulse therapy

Received: March 20 1997
Accepted after revision July 31 1998

Preliminary data was presented during the ERS Meeting in Stockholm in 1996.

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with a poor response to therapy and a prognosis similar to malignancies; the 5-yr survival rate is estimated at only 50% [1–4]. The pathogenesis of IPF involves abnormalities in the complex pathways of the immune system [2, 5]. Therefore, most drugs used in IPF are immunosuppressive agents. Corticosteroids are widely used for initial treatment, with response rates between 15 and 50% [1, 5, 6]. Many other substances have been used but none has shown better efficacy. Cyclophosphamide and azathioprine have been reported to be of some value in IPF [7–9]; however, most studies demonstrating benefits were conducted in small patient populations. In case of deterioration despite corticosteroid therapy, clinicians hesitate to use a potentially harmful drug with uncertain efficacy. In this study, experience with cyclophosphamide in IPF is reported. The intravenous intermittent pulse therapy was preferred over a daily oral regimen because of less drug-related toxicity [10, 11]. Side-effects were carefully monitored and a subgroup of patients was identified that appeared to benefit from this type of therapy.

Methods

Study population

Eighteen patients (10 females and eight males) with progressive IPF were treated for 1 yr with *i.v.* cyclophosphamide. After 1 yr, cyclophosphamide was stopped and treatment was continued with the achieved dose of prednisolone. The mean age was 59 yrs (range 36–75 yrs) and the mean duration of disease prior to treatment was 28.2 months (range 6–90). The diagnosis was made using established clinical and radiological criteria [8, 12]: breathlessness, presence of fine crackles, especially in the bases, and diffuse interstitial shadowing on chest radiography. Interstitial lung disease of known or other unknown causes was carefully excluded. Fifteen patients had undergone high-resolution computed tomography (HRCT) with findings consistent with IPF. Histological examination of lung tissue was performed in all patients (transbronchial biopsy in 13 and open biopsy in five patients, in whom transbronchial biopsy was insufficient). Table 1 summarizes the patient characteristics. Patients had received prednisolone

Table 1. – Characteristics of the study group before cyclophosphamide pulse therapy

Subject No.	Sex	Age yrs	Smoking history never-/exsmoker	Disease duration months	Initial VC L (% pred)	Initial P_{a,O_2} mmHg	Prednisolone mg·day^{-1}	BAL differential cell count %			
								AM	N	E	L
1	F	57	Never	36	2.2 (71)	57.5	30	55	3	0	42
2	M	36	Never	15	2.1 (51)	50.1	40	26	15	0	59
3	M	45	Ex	8	2.9 (57)	90.0	40	46	14	15	25
4	F	65	Ex	30	1.3 (49)	64.7	30	42	16	1	40
5	M	60	Never	13	2.8 (59)	66.7	60	42	14	1	43
6	F	70	Never	6	1.8 (73)	62.6	20	ND	ND	ND	ND
7	F	65	Never	24	2.3 (77)	51.9	25	28	48	1	23
8	F	75	Never	30	1.1 (48)	61.8	20	38	46	0	16
9	F	66	Never	7	1.7 (63)	66.0	20	38	6	1	55
10	F	57	Never	47	1.4 (50)	64.4	10	49	27	5	19
11	M	64	Ex	15	2.8 (63)	85.5	15	17	62	4	17
12	F	60	Never	90	1.1 (40)	52.7	10	67	20	3	10
13	M	45	Never	60	1.9 (44)	71.0	70	71	3	3	23
14	M	57	Ex	7	2.9 (63)	79.5	60	56	19	10	15
15	F	65	Never	7	1.2 (43)	54.8	60	ND	ND	ND	ND
16	F	56	Never	67	0.8 (27)	78.6	10	27	56	0	17
17	M	57	Never	7	0.9 (32)	69.3	75	ND	ND	ND	ND
18	M	56	Ex	38	1.2 (33)	73.2	30	54	41	0	5

Patient number 12 was excluded from the treatment group owing to repeated pneumonia. VC: vital capacity; % pred: percentage of predicted value; P_{a,O_2}: arterial oxygen tension ; BAL: bronchoalveolar lavage; AM: alveolar macrophages; N: neutrophils; E: eosinophils; L: lymphocytes; F: female; M: male. (1 mmHg=0.133 kPa.)

therapy for at least 3 months (dosage between 0.5 and 1.5 mg·kg body weight^{-1}) with no effect on the clinical course or had had a relapse after tapering corticosteroids. Six patients had taken prednisolone for 3 months, seven patients for 4–9 months, three patients had received two or three courses of high-dose prednisolone and two patients had received additional azathioprine for 3 and 4 months each.

Study design

This study is a retrospective analysis of experiences with *i.v.* cyclophosphamide in IPF. Because this therapy was chosen for patients in whom conventional treatment with corticosteroids had failed, no control group is available. The treatment protocol was similar to that of other authors [8] and modified as follows: a starting dose of 500 mg cyclophosphamide (Endoxan; Asta Medica, Frankfurt, Germany) was given *i.v.* for 1 h in 1,000 mL 0.9% saline solution, and was increased by 100 mg every 2 weeks to a total of 1,000–1,300 mg (15 mg·kg body weight^{-1}). This dose was repeated once a month for 1 yr. Before infusion of cyclophosphamide 400 mg, mesna was given *i.v.* (Uromitexan; Asta Medica). Patients also received 0.5 mg prednisolone·kg body weight^{-1}·day^{-1}, which was gradually tapered as much as possible after the first 6 weeks of therapy.

Patients were followed for a minimum of 14 months or until death. Vital capacity (VC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC) and gas transfer factor were measured before infusion by a body plethysmograph (Bodytest and Alveo-Diffusionstest; E. Jaeger, Würzburg, Germany). Blood from an arterialized ear lobe was analysed for oxygen (P_{a,O_2}) and carbon dioxide (P_{a,CO_2}) (Blood gas analyzer; Radiometer, Copenhagen, Denmark). Clinical symptoms, such as dyspnoea, cough plus sputum quantity and indicators of general health, were noted and a physical examination was performed. At each visit patients were advised about the dosage of additional corticosteroids, which were prescribed by the responsible physician according to the clinical course. For evaluation, patients were classified as improved, stable disease or nonresponders according to changes in VC, P_{a,O_2} and reduction of additional corticosteroids, as well as changes in clinical symptoms at 1 yr of treatment [13]. The criteria used for classification are given in table 2. For assignment to one of the three groups, three out of four criteria had to be fulfilled (patient number 5 was classified as improved although VC and P_{a,O_2} only stabilized, as the patient clearly improved clinically).

Because bone marrow depression and infections were anticipated as potential side-effects, patients were carefully monitored. Blood cell counts were taken weekly and cyclophosphamide dosage was reduced or delayed if leukocytes were <3,000·μL^{-1} or platelets were <80,000·μL^{-1}, respectively. Chest radiography was performed after 4 months and when infection of the respiratory system was presumed. In cases of infection, treatment with antibiotics was initiated and immunosuppression delayed until symptoms had completely disappeared. Patients with life-threatening infections were excluded from the protocol.

Table 2. – Criteria used for the classification of the response to cyclophosphamide pulse therapy*

	Improvement	Stabilization	Progression
VC difference %	>10	>-10, <10	<-10
P_{a,O_2} difference mmHg	>10	>-10, <10	<-10
Prednisolone difference mg·day^{-1}	>10	<10	Not possible
Clinical symptoms	Improved	Stable	Deteriorating

*: After 1 yr of treatment, three out of four criteria had to be fulfilled. VC: vital capacity; P_{a,O_2}: arterial oxygen tension. (1 mmHg =0.133 kPa.)

Statistical analysis

The nonparametric Mann–Whitney U-test was used for comparing two groups of quantitative data. Data are shown as mean±SD or the range of single values. For comparison of parameters within groups, Chi-squared analysis was used. The reduction in daily prednisolone after 1 yr was analysed by the Wilcoxon test. Statistical significance was assumed at the 5% level. STASY® software was used to analyse the data (Fa. Pic, München, Germany).

Results

Eighteen patients with progressive IPF were treated as described above. Patient number 12 developed two episodes of pneumonia during the first 6 months of cyclophosphamide treatment and, therefore, was withdrawn from further cyclophosphamide therapy and from evaluation of efficacy after 1 yr. Changes in lung function, P_{a,O_2} and the need for additional corticosteroids are given in table 3. Following 1 yr of treatment, VC was improved in three patients by >10% (compared with the pretreatment value), while it remained stable in eight and decreased in six by >10%. According to the response criteria (table 2), six patients showed improvement, five remained stable and six deteriorated (table 3). The change in VC was +12.9±22.3% after 1 yr in the first, -0.2±7.7% in the second and -20.7± 18.2% in the third group. There was no significant change in TLC. The transfer factor was not regularly measured in all patients and was not evaluated. P_{a,O_2} increased by +0.40±1.08 kPa (+3.0±8.1 mmHg) in improving patients, was -0.20±0.51 kPa (-1.5±3.8 mmHg) in stable patients and decreased by 2.08±1.92 kPa (15.6±14.4 mmHg) in progressive patients.

Patients with improvement and those with stable disease were pooled and termed responders, while the group with progressive disease was termed nonresponders. The change in VC was +6.7±17.9% in responders and -20.6± 18.2% in nonresponders (p=0.008). The change in P_{a,O_2} was 0.12±2.43 kPa (0.9±18.2 mmHg) in responders and -2.08±1.92 kPa (-15.6±14.4 mmHg) in nonresponders (p= 0.008).

Oral corticosteroids were reduced in all 17 patients who were treated for 1 yr, from 34.7±21.5 to 17.9±21.9 mg prednisolone·day^{-1} (p=0.001). Responders were able to reduce daily prednisolone by 19.1±13.4 mg (nonrespond-ers by 6.7±16.3 mg; p=0.02), responders with improved parameters from 36.7±13.7 to 9.0±6.0 mg (p=0.01) and responders with stable disease from 25.0±20.0 to 13.2±5.4 mg (p=0.03). The reduction in the nonresponder group was not significant (from 50.8±25.4 to 41.0±29.4 mg; p=0.15) (fig. 1). The therapeutic benefit was maintained for at least 3 months after cessation of cyclophosphamide pulse therapy.

Responders had a significantly higher percentage of lymphocytes in bronchoalveolar lavage (BAL) than nonresponders (34±16 *versus* 15±8%; p=0.017) (table 4). Patients who responded to therapy had a greater initial VC than the nonresponders. The initial VC was 2.0±0.6 and 1.5±0.79 L, respectively (p=0.02). Eight out of nine patients with a VC of >50% predicted responded to therapy, whereas only three out of eight with a VC <50% pred responded (p=0.03, Chi-squared test). This correlated with a decreased duration of symptoms: seven out of eight patients with a disease duration of >28 months had an initial VC <50% pred and eight out of nine patients with a VC >50% pred had a shorter course (p=0.004, Chi-squared test). Because of the large standard deviation of values there was no significant difference between the mean duration of symptomatic disease before cyclophosphamide therapy between the two groups (responders 21±13 *versus* nonresponders 31±28 months). Responders tended to be older than nonresponders (60±11 and 56±6 yrs, respectively). The latter had received significantly higher doses of prednisolone before cyclophosphamide pulse therapy (50.8 *versus* 28.2 mg; p=0.04). No correlation with smoking history was observed.

Table 3. – Changes in the study group after 1 yr of cyclophosphamide pulse therapy

Subject No.	VC difference %	P_{a,O_2} difference mmHg	Prednisolone difference mg·day^{-1}	Clinical symptoms dyspnoea/cough/ state of health	Survival since first pulse months	Classification
1	-14.1	13.9	20	±/+/+	48	R
2	-2.3	10.8	30	+/+/+	22	R
3	41.1	-0.2	36	+/±/+	45	R
4	27.8	2.2	25	+/-/+	33*	R
5	-3.6	-8.0	40	+/+/+	35	R
6	28.4	-1.0	15	+/+/+	20	R
7	-12.6	3	25	+/0/+	49	S
8	-0.9	-3.7	5	+/+/+	14	S
9	1.2	-1.3	10	±/±/+	17	S
10	8.0	1.3	4	±±/±/-	27	S
11	3.2	-6.6	0	±/±/+	19	S
12	-53.9	-15.1	10	+/0/+	48	0
13	2.6	-9.3	0	-/-/-	3*	NR
14	-44.8	-23.0	40	±/±/+	14*	NR
15	-33.8	-18.5	0	-/±/-	4*	NR
16	-13.5	-24.6	0	-/0/-	3*	NR
17	-5.4	-28.8	0	-/±/-	3*	NR
18	-29.0	10.5	0	-/-/-	4*	NR

Clinical symptoms are shown as improved (+), stable (±) or progressive (-); 0: did not occur. *: patient has died. Patient number 12 was withdrawn from the treatment group owing to repeated pneumonia. VC: vital capacity; P_{a,O_2}: arterial oxygen tension; R: response; S: stability; NR: nonresponse. (1 mmHg=0.133 kPa.)

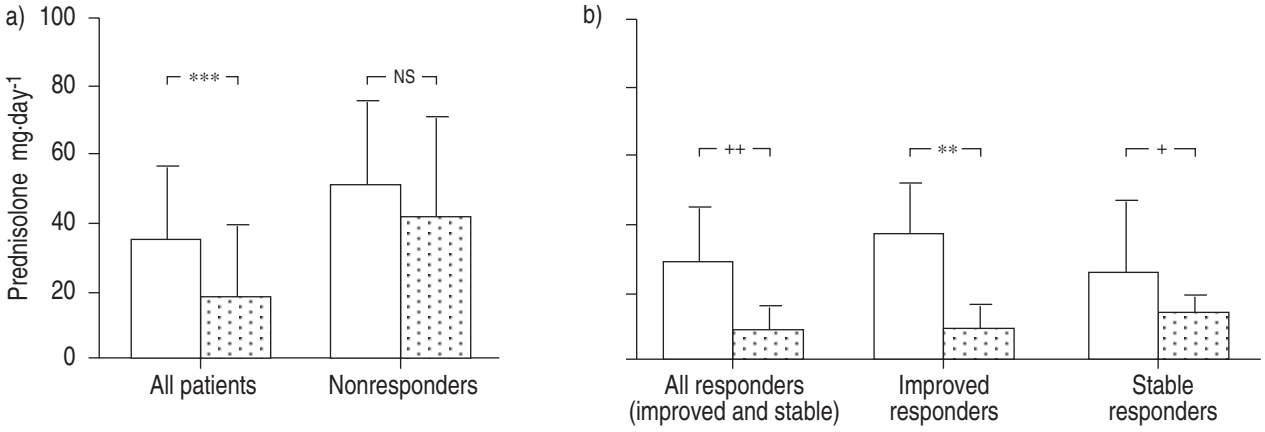

Fig. 1. – Reduction in additive daily prednisolone in the whole study group and in different subgroups after 1 yr of cyclophosphamide pulse therapy (mean±SD). ▭: before initiation of treatment; ▦: after 1 yr. +: p=0.03; **: p=0.01; ++: p=0.003; ***: p=0.001; NS: nonsignificant difference between groups.

Seven patients died after the initiation of cyclophosphamide therapy (table 3). In five patients this was due to a rapid progression of disease: four patients died of respiratory failure due to IPF and one patient (number 13) died of pneumonia. All patients who survived the first 4 months received cyclophosphamide for 1 yr. One patient died of respiratory failure due to IPF 3 months after the end of pulse therapy (number 14) and another (number 4) died after 21 months from suicide.

The most threatening side-effect of immunosuppression is infectious disease. Eight cases of upper respiratory tract infections occurred, characterized by cough, pharyngitis and yellow sputum (patients numbers 1, 3, 5, 7, 8, 10, 11 and 14). Five pneumonias with additional fever and opacities on chest radiography were observed (patients numbers 10, 12 (twice), 13 and 17). Patients numbers 10 and 12 experienced at least one pneumonia more than 6 months after termination of cyclophosphamide treatment. Patient number 13 died of pneumonia, all other infectious complications were treated successfully with antibiotics. Patient number 1 had a mild episode of bacterial cystitis, but chemical urocystitis was not observed in any patients. Mild leukopenia was common, as was mild anaemia, but leukocyte counts never fell below 3,000·uL^{-1}. There was no correlation between leukocyte counts and infectious complications. Nausea and alopecia were mild to moderate.

Table 4. – Characteristics of the responder (improved and stable) and nonresponder subgroups

	Responders	Nonresponders	p-value
n	11	6	
Sex Female	7/9	2/9	NS
Male	4/8	4/8	NS
Age yrs	60±11	56±6	NS
VC initial L	2.0±0.6	1.5±0.8	0.02
% pred	60.2±10.2	40.3±12.9	0.004
Prednisolone before pulse mg	28.2±14.2	50.8±25.4	0.04
BAL Lymphocytes %	34±16	15±8	0.02
Neutrophils %	25±20	30±23	NS
Disease duration months	21±13	31±28	NS

VC: vital capacity; % pred: percentage of predicted value; BAL: bronchoalveolar lavage; NS: nonsignificant.

Discussion

In this study objective benefits were seen in a subgroup of 17 patients with IPF treated with 1,000–1,300 mg *i.v.* cyclophosphamide given at monthly intervals. Deterioration in VC was arrested in 11 (61%) patients, three (27%) of whom improved by >10%. All patients with progressive disease despite therapy died within the follow-up period. Regarding the course of VC, P_{a,O_2}, clinical symptoms and additional need for corticosteroids, a group of 11 patients was determined whose progression of disease was arrested and six who further deteriorated. Response to treatment was defined as improvement or at least stability of the respiratory situation. The first positive effects of treatment were noticed 2–4 months after initiation and were still present 3 months after the preliminary end-point of 1 yr.

The benefit of cytotoxic agents in IPF is discussed controversially. Clinical data are lacking, most studies are retrospective and patient groups are small. Cyclophosphamide has been used successfully in interstitial lung disease complicating collagen vascular disease, especially systemic sclerosis, lupus erythaematodes and polymyositis [14–18]. One of the few prospective trials comparing prednisolone alone with cyclophosphamide plus prednisolone in IPF, published by JOHNSON *et al.* [7] in 1989, showed no sig-nificant benefit for cyclophosphamide over prednisolone alone. A trend toward an improvement was, however, observed: after 1 yr of treatment, 57% of patients in the combined group improved or stabilized, compared with only 32% in the prednisolone group. The patients who did not respond to therapy were switched to the other group, with a clear advantage for the cyclophosphamide plus prednisolone group. However, this benefit was limited by the toxicity of cyclophosphamide, which led to the reduction and eventually cessation of treatment after 2–3 yrs in seven patients.

The long-term toxicity of cyclophosphamide is dependent on the cumulative dose [10]. Data show that intermittent, intravenous doses are equally effective and better tolerated than daily oral doses [10, 11, 19]. Based on the experience with intermittent cyclophosphamide in collagen vascular disease and vasculitis, BAUGHMAN and LOWER [8]

treated 33 patients with IPF by administering 1,000–1,800 mg cyclophosphamide every 2 weeks for up to 18 months. Patients who survived for >6 months showed a significant improvement in forced vital capacity (FVC), which was maintained for the following year. In addition, prednisolone reduction was possible from 32 to 4 mg· day^{-1}.

The present study was designed according to the protocol of BAUGHMAN and LOWER [8] and led to similar results. The stabilization of VC seems to be related to enhanced survival [20]. However, besides spirometric data, clinical and radiological criteria should also be considered in the course of IPF [21]. These criteria were used to define the responder and nonresponder groups. An important marker of response to cyclophosphamide treatment is, in the authors' opinion, the reduction of the dose of corticosteroid. In this study the daily prednisolone dose could be reduced by approximately 50% in the whole group (from 34.7 to 17.9 mg). This was even more obvious in the majority of responders, in whom prednisolone was reduced by 76% (from 36.7 to 9.0 mg). Because corticosteroid related myopathy and osteoporosis may further compromise patients with chronic pulmonary disease, this reduction of corticosteroids is potentially important. In addition, in most lung transplantation centres, IPF patients on high dose oral corticosteroid regimens are excluded from this remaining therapy [8].

The VC of responders was significantly better than that of progressive patients at initiation of therapy (60.2 *versus* 40.3% pred), which was due to a shorter duration of disease. Similar observations were reported by JOHNSON *et al.* [7]: patients in the combined cyclophosphamide/prednisolone group with a TLC between 60 and 79% pred had a significantly longer stabilization of their disease course than the prednisolone group. In contrast, patients with TLC <60% pred did not differ. This observation may indicate that immunosuppressive therapy with cyclophosphamide should be initiated early. Accordingly, VAN OORTEGEM *et al.* [22] reported an increased likelihood of treatment response if disease duration is shorter. Assuming that IPF is a progressive inflammatory disease leading to irreversible fibrosis within months to years, it is likely that immunosuppressive treatment in the early stage is more promising than in the late stage of fibrosis.

A significantly higher percentage of lymphocytes are seen in BAL of responders than in nonresponders (34 *versus* 15%). It is known that lymphocytic alveolitis shows a more favourable response to corticosteroids than neutrophilic or eosinophilic inflammation [3, 23–25]. However, some investigators have also reported a positive influence of cyclophosphamide on the latter [8, 24]. Because only two patients in the present study showed a clear increase in eosinophils in BAL, this hypothesis can be neither confirmed nor rejected.

Intermittent intravenous administration of cyclophosphamide in IPF was well tolerated. The most dangerous side-effects are infectious complications, especially upper and lower respiratory tract infections, which led to the termination of therapy in one patient in this study. At least one patient died because of final pneumonia. Although this is a recognized complication of terminally ill IPF patients [2, 5, 26], it cannot be excluded that these pneumonias were induced by treatment, since cyclophosphamide is known to cause sustained immunosuppression (reviewed in [27]). In contrast to the clear advantage in reducing long-term toxicity [10, 11], intermittent administration of cyclophosphamide is not superior to the daily regimen regarding infectious complications [27]. The present data show 14 episodes of infection during 240 patient-months of cyclophosphamide treatment, but all except one were successfully treated with antibiotics. Another investigation dealing with infectious complications in Wegener's granuloma-tosis treated with a combined regimen of daily cyclo-phosphamide and corticosteroid reports about 17 clinical episodes of infection over 201 patient-months [28]. Intermittent administration in 12 patients with lupus nephritis resulted in three serious infections in 1 yr [19]. Little in-formation about treatment-related infections in IPF is provided in the literature. Neither BAUGHMAN and LOWER [8] nor JOHNSON *et al*. [7] reported about any infection during intermittent or daily cyclophosphamide therapy in IPF. Because of the higher incidence of pneumonias in IPF, even without treatment, this raises some doubt [2, 5, 26]. Nevertheless, the incidence of respiratory tract infections is quite high and demands close follow-up of patients. No carcinogenic effects of cyclophosphamide were observed in the present trial, perhaps because of the short duration of follow-up and the small patient population.

From this retrospective study, it can be concluded that intermittent intravenous immunosuppression by cyclophosphamide is a well-tolerated therapy in progressive idiopathic pulmonary fibrosis not responding to corticosteroids alone. An attempt was made to characterize those patients in whom therapy was beneficial. Similar to corticosteroid treatment, a shorter course of disease (characterized by a vital capacity of >50% predicted) and a higher percentage of bronchoalveolar lavage lymphocytes was associated with a better response to pulsed cyclophosphamide therapy. If corticosteroids fail to stop disease progression, a trial of intermittent cyclophosphamide combined with corticosteroids is recommended in these patients. Because of potentially life-threatening side-effects, close surveillance of patients is necessary.

Acknowledgements: The authors thank B. Allolio for his critical review of the manuscript and M. Wechner for general technical support.

References

1. Carrington CB, Gaensler EA, Coutu RE, *et al.* Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978; 298: 801–809.
2. Meier-Sydow J, Weiss SM, Buhl R, Rust M, Raghu G. Idiopathic pulmonary fibrosis: current clinical concepts and challenges in management. *Semin Respir Crit Care Med* 1994; 15: 77–96.
3. Rudd RM, Haslam PL, Turner-Warwick M. Cryptogenic fibrosing alveolitis: relationships of pulmonary physiology and bronchoalveolar lavage to response to treatment and prognosis. *Am Rev Respir Dis* 1981; 127: 1–8.
4. Cherniack RM, Crystal RG, Kalica AR. Current concepts in idiopathic pulmonary fibrosis: a road map for the future. *Am Rev Respir Dis* 1991; 143: 680–683.
5. Meyer KC, Raghu G. Perspectives and future advances on the diagnosis and treatment of idiopathic pulmonary fibrosis. *In*: Pulmonary Fibrosis. Lung Biology in Health and Disease, Vol. 80. New York, Marcel Dekker, 1995;

pp. 837–871.
6. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. *Thorax* 1980; 35: 171–180.
7. Johnson MA, Kwan S, Snell JC, Nunn AJ, Darbyshire JH, Turner-Warwick M. Randomized controlled trial comparing prednisone alone with phosphamide and low dose prednisone in combination in cryptogenic fibrosing alveolitis. *Thorax* 1989; 44: 280–288.
8. Baughman RP, Lower EE. Use of intermittent intravenous cyclophosphamide for idiopathic pulmonary fibrosis. *Chest* 1992; 102: 1090–1094.
9. Raghu G, Depaso WJ, Cain K, *et al.* Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991; 14: 291–296.
10. Cupps TR. Cyclophosphamide: to pulse or not to pulse? *Am J Med* 1990; 89: 399–402.
11. Austin HA, Kippel JH, Balon JE, *et al.* Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic fibrosing drugs. *N Engl J Med* 1986; 313: 614–619.
12. Haslam PL, Turton CWG, Lukoszek A, *et al.* Bronchoalveolar lavage cell counts in cryptogenic fibrosing alveolitis and their relations to therapy. *Thorax* 1980; 35: 328–339.
13. Mortenson RL, Panos RJ, King TE Jr. Idiopathic pulmonary fibrosis. *In*: Bone RC, ed. Pulmonary and Critical Care Medicine. Vol. M. St Louis, MO, Mosby Year Book, 1993; pp. 1–14.
14. Al-Janadi M, Smith CD, Karsh J. Cyclophosphamide treatment of interstitial pulmonary fibrosis in polymyositis/dermatomyositis. *J Rheumatol* 1989; 16: 1592–1596.
15. Weese WC, Levine BW, Kazemi H. Interstitial lung disease resistant to corticosteroid therapy: report of three cases treated with azathioprine or cyclophosphamide. *Chest* 1975; 67: 57–60.
16. Boulware DW, Makkena R. Monthly cyclophosphamide in lupus pneumonitis and myositis. *J Rheumatol* 1991; 18: 153.
17. Steen VD, Lanz JK, Conte C, Owens GR, Medsger TA. Therapy for severe interstitial lung disease in systemis sclerosis. *Arthritis Rheum* 1994; 37: 1290–1296.
18. Silver RM, Warrick JH, Kinsella MB, Staudt LS, Baumann MH, Strange C. Cyclophosphamide and low dose prednisone in patients with systemic sclerosis (scleroderma) with interstitial lung disease. *J Rheumatol* 1993; 20: 838–844.
19. Valeri J, Radhakrishnan D, Estes D, *et al.* Intravenous pulse cyclophosphamide treatment of severe lupus nephritis: a prospective five-year study. *Clin Nephrol* 1994; 42: 71–78.
20. Hanson D, Winterbauer RH, Kirtland SH, Wu R. Changes in pulmonary function test results after 1 year of therapy as predictors of survival in patients with idiopathic pulmonary fibrosis. *Chest* 1995; 108: 305–310.
21. Watters LC, King TE, Schwarz MI, Waldron JA, Stanford RE, Cherniack RM. A clinical, radiographic and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1986; 133: 97–103.
22. Van Oortegrem K, Wallaert B, Marquette CH, *et al.* Determinants of response to immunosuppressive therapy in idiopathic pulmonary fibrosis. *Eur Respir J* 1997; 7: 1950–1957.
23. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. *Thorax* 1980; 35: 593–599.
24. Turner-Warwick M, Haslam P. The value of serial bronchoalveolar lavages in assessing the clinical progress of patient with cryptogenic fibrosing alveolitis. *Am Rev Respir Dis* 1987; 135: 26–34.
25. Watters LC, Schwarz MI, Cherniak RM, *et al.* Idiopathic pulmonary fibrosis: pretreatment bronchoalveolar lavage cellular constituents and their relationships with lung histopathology and clinical response to therapy. *Am Rev Respir Dis* 1987; 135: 696–704.
26. Panos RJ. Therapy and management of idiopathic pulmonary fibrosis. *Compr Ther* 1994; 20: 289–293.
27. Lynch JP, McCune WJ. Immunosuppressive and cytotoxic pharmacotherapy for pulmonary disorders. *Am J Respir Crit Care Med* 1997; 155: 395–420.
28. Bradley JD, Brandt KD, Katz BP. Infectious complications of cyclophosphamide treatment for vasculitis. *Arthritis Rheum* 1989; 32: 45–53.