Usefulness of Cyclophosphamide Pulse Therapy in Interstitial Lung Diseases

Jonas Christian Schupp Thomas Köhler Joachim Müller-Quernheim

Department of Pneumology, University Medical Centre, Albert Ludwig University, Freiburg, Germany

Key Words

Interstitial lung disease · Idiopathic pulmonary fibrosis · Lymphocytic interstitial pneumonia · Cyclophosphamide

Abstract

Background: Interstitial lung diseases (ILDs) are a group of disorders characterised by progressive lung function decline. Stabilisation of lung function under intermittent i.v. cyclophosphamide was shown in patients suffering from systemic sclerosis, yet data in ILD patients are scarce. **Objectives:** To retrospectively evaluate the usefulness of cyclophosphamide pulse therapy in ILD. **Methods:** We retrospectively analysed all patients who received i.v. cyclophosphamide in our centre from 2002 to 2012. Lung function, survival status, and bronchoalveolar lavage cytology were recorded during a follow-up period of 18 months. **Results:** Twenty-six patients with idiopathic pulmonary fibrosis, 6 with lymphocytic interstitial pneumonia (LIP), 8 with idiopathic non-specific interstitial pneumonia (NSIP), 7 with rheumatoid arthritis-associated ILD, and 7 with perinuclear anti-neutrophil cytoplasmic antibody-positive ILD (pANCA+ ILD) were included. Patients with LIP and NSIP had the best survival outcome, those with pANCA+ ILD the worst. In the total cohort, we found a significantly higher total lung capacity decline in the year before treatment compared to the year after treatment. **Conclusions:** This retrospective analysis of cyclophosphamide treatment shows a stabilisation of lung function in most patients with fibrotic ILDs, yet prospective studies in clearly defined diagnoses are urgently needed.

© 2016 S. Karger AG, Basel

Introduction

Interstitial lung diseases (ILDs) are a group of diseases characterised by progressive lung function decline, but with different aetiologies and different clinical courses [1, 2]. They consist of different pathogenic syndromes, such as rheumatologic or occupational disorders, or are idiopathic [3, 4]. Treatment recommendations are usually of low evidence, as double-blinded, randomised and prospective studies in ILDs are sparse. In our referral centre, cyclophosphamide is prescribed as second-line therapy in inflammatory and progressive fibrotic ILD, resulting in the opportunity of a retrospective analysis.

Nowadays, immunosuppression in idiopathic pulmonary fibrosis (IPF) has been observed to be contraindicated by most clinicians, as the treatment arm of the PANTHER trial, comparing prednisone, azathioprine, and N-acetylcysteine with placebo, resulted in an increased risk of death and hospitalisation [5]. The main driver of mortality was respiratory worsening; the main causes of hospitalisation were infectious and respiratory ones. Furthermore, in a case-control-study, Collard et al. [6] found no difference in the survival of IPF patients, whether they were treated with oral cyclophosphamide and corticosteroids or not. As both intervention groups attended different medical centres, other factors, be they environmental or socio-economic, might have had some influence as well. Yet, in several uncontrolled open-label studies, treatment of IPF patients with i.v. cyclophosphamide led to a stabilisation of lung function and/or im-

provement of survival, as compared to treatment with steroids or azathioprine [7–9]. Although new effective drugs for IPF (pirfenidone and nintedanib) are now available, about 15–20% of patients treated with these new drugs will suffer from progressive disease [10–13]. Thus, there is still an urgent need for an evaluation of further therapeutic options.

In contrast to IPF, immunosuppression still remains the most important course of action in inflammatory ILDs, and in most cases, a clearer treatment success is to be noted compared to fibrotic ILDs [14]: treatment of lung involvement of rheumatoid arthritis, when corticosteroids are not sufficient, usually consists of mycophenolate or rituximab, or in case of extensive or rapidly progressing lung disease of cyclophosphamide pulse therapy [15]. In cellular idiopathic non-specific interstitial pneumonia (NSIP), treatment with corticosteroids is usually sufficient, whereas patients with fibrotic NSIP may not respond to a steroid medication alone and require further therapy: the most widely used further immunosuppressant drugs are azathioprine, colchicine, and cyclophosphamide [16]. In anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, standard care used to be steroids and cyclophosphamide for induction therapy, and steroids and azathioprine for maintenance therapy. Yet, mainly since the RAVE [17] and the MAINRITSAN [18] studies, rituximab has become a reasonable treatment option in induction as well as in maintenance therapy. Lymphocytic interstitial pneumonia (LIP) is poorly understood, and there exist no controlled treatment trials. Usually, patients respond well to corticosteroids alone. The most widely used second-line treatment options are azathioprine, cyclosporine A and cyclophosphamide [19].

Taken together, published data on cyclophosphamide treatment in ILD are scarce. However, due to reduced prescription rates of immunosuppressive drugs after the premature termination of the azathioprine arm of the PANTHER study [5], we saw the need for an analysis of our past therapeutic approach. Therefore, we retrospectively analysed the cohort of ILD patients treated with cyclophosphamide in our centre in the last decade.

Methods

We retrospectively included all patients who received cyclophosphamide in our centre from 2002 to 2012 by analysing the delivery orders of our pharmacy. Patients who had less than 3 infusions of cyclophosphamide were excluded to avoid situations where cyclophosphamide was used as rescue medication (e.g. at

the intensive care unit). All patients had been diagnosed according to the most recent criteria [1, 20] in a synopsis of clinical, pathological, and radiological findings. All included patients were treated according to a modified AUSTIN protocol [21] and were planned to receive 500–1,000 mg of cyclophosphamide and 600 mg of urometixan monthly for a total of 6 infusions. Before each infusion, renal and hepatic function and a differential hemogram were evaluated. As add-on therapy, patients received oral corticosteroids, either continuing an existing oral steroid medication or starting with oral prednisone 0.5–1 mg/kg body weight daily. If the patients showed signs of infection or lymphocyte counts $<1,000/\mu\text{l}$, cyclophosphamide infusions were postponed until the cause was resolved. Only disorders with at least 5 patients to be analysed were included. During the routine follow-up visits, pulmonary function tests (PFTs) were carried out according to the ATS/ERS recommendations [22, 23]. A decline of $\leq -10\%$ of the forced vital capacity (FVC) % predicted or total lung capacity (TLC) % predicted was considered a relevant progression of ILD. Bronchoscopy, bronchoalveolar lavage (BAL) of 300 ml and counting of BAL cells was carried out as described earlier [24]. Patients were followed up a maximum of 18 months for vital status and pulmonary function testing. Vital status was determined by follow-up visits at our referral centre, by telephone calls to the patient, family members or the general practitioner, or by contacting the registry office. This retrospective analysis was approved by the Ethics Committee of the University of Freiburg (No. 10009/15).

Statistical Analysis

Values are expressed as means $\pm$ standard deviation. To compare patient's characteristics, Fisher's exact test for categorical measures and the Mann-Whitney U test for continuous measures were used. We computed Kaplan-Meier curves to analyse the treatment effect. A statistical significance level of 0.05 was used throughout.

Results

Study Population

Twenty-six patients with IPF, 6 with LIP, 8 with idiopathic NSIP, 7 with rheumatoid arthritis-associated ILD (RA-ILD), and 7 with perinuclear ANCA-positive ILD (pANCA+ ILD) were included. Pre-treatment usually included steroids (for values, see table 1) and other immunosuppressants (mainly azathioprine, leflunomide, cyclosporine, and mycophenolate). Four of the IPF patients have participated in a clinical trial (INSPIRE, AVIPTADIL, and BUILD study) as pre-treatment. Sixteen patients died during the follow-up and 11 suffered from progression of their underlying lung disease. LIP patients had the best TLC and diffusing capacity of the lung for carbon monoxide (DLCO) at the time point of treatment initiation, whereas the mean PFT of the other disease groups did not differ. In LIP and pANCA+ ILD,

Table 1. Demographic characteristics

	IPF	NSIP	LIP	pANCA+ ILD	RA-ILD
Gender, n					
Female	4	3	5	5	1
Male	22	5	1	2	6
Age, years	63.5±11.4	62.9±8.5	67.5±5.6	55.6±12.4	63.1±7.0
Smoking history, n					
Active	0	0	0	0	0
Former	15	3	3	2	4
Never	11	5	3	5	3
Pretreatment, %					
Steroids	69	100	67	71	100
Other immunosuppressant	46	63	50	29	71
TLC, % predicted	54.4±11.5	48.4±6.1	72.8±25.7	50.7±13.1	49.3±10.5
FVC, % predicted	60.0±16.7	51.9±12.4	69.1±22.0	46.4±18.8	54.6±12.2
FEV ₁ , % predicted	59.8±13.8	49.3±12.3	58.6±15.5	46.1±19.9	55.5±13.4
DLCO, % predicted	35.6±16.9 (n = 15)	35.6±8.1 (n = 4)	79.3±38.3 (n = 3)	missing	30.8±16.5 (n = 3)
Cell count/100 ml BAL, ×10 ⁶	23.8±23.4	13.6±9.8	15.8±7.3	15.5±14.1	20.6±19.2
Alveolar macrophages, %	58.4±25.7	55.7±19.8	57.0±20.5	46.5±23.8	47.0±32.7
Lymphocytes, %	13.1±15.4	17.3±12.7	27.6±17.5	13.3±12.5	20.0±26.9
Neutrophil granulocytes, %	19.1±16.7	22.7±15.3	12.6±11.5	33.7±30.7	27.6±34.4
Eosinophil granulocytes, %	8.5±6.5	4.2±3.3	2.8±2.3	6.0±4.1	4.4±2.4

FEV₁ = Forced expiratory volume in 1 s.

a predominance of female patients was noted, in contrast to IPF, NSIP, and RA-ILD, where male patients were most prominent. Patients with pANCA+ ILD were younger compared to the remaining patients. In 39 patients (72%), recent (0–183 days, median 23 days, before the start of therapy) BAL cytology data were available. BAL cytology showed lymphocytosis in LIP and RA-ILD as well as neutrophilia in IPF, NSIP, pANCA+ ILD, RA-ILD, and in LIP. BAL eosinophilia was most prominent in IPF and pANCA+ ILD (table 1).

Cyclophosphamide Treatment

The mean initial dosage was 759 mg (±167 mg) cyclophosphamide. Thirty-six of 54 patients (66.7%) received 6 infusions of cyclophosphamide as planned in advance. Patients received a mean of 5.3 infusions. A total of 96% of patients also received steroids, with a mean prednisolone (or equivalents) dosage of 19 mg (±12 mg). Discontinuation of treatment occurred due to the following reasons: infections (n = 7), unknown reasons (n = 6), persistent leukopenia (n = 1), disease progression under cyclophosphamide (n = 1), patient request (n = 1), new contraindication due to accident (n = 1), and change to oral medication (n = 1).

Lung Function Analysis

PFT data of 18 patients approximately 1 year before, at, and after the beginning of treatment were available. A complete lung function time course of the remaining patients was missing due to two reasons. First, some patients were treated in advance elsewhere before they were referred to our centre. Second, 16 patients died during the follow-up, and therefore, a lung function test could not be performed. Missing data were not imputed. We calculated the annual TLC decline for every patient. In the total cohort, we found a significantly higher TLC decline in the year before treatment (–11.4% per year) compared to the year after treatment (+1.8% per year, *p* = 0.007; fig. 1). FVC time course showed a non-significant trend towards reduction of FVC decline (–7.8 vs. –1.8% per year, *p* = 0.09). In the subgroup of IPF patients (n = 7), the annual TLC change (–10.3 vs. +0.7% per year) and the annual FVC change (–15.6 vs. –0.1% per year) were not significant, probably due to the small sample size (fig. 1).

Survival Analysis

The patients were followed up for 18 months. Survival clearly differed between disease groups: patients with LIP and NSIP had the best outcome, those with

Fig. 1. Adjusted annual TLC decline. Adjusted annual TLC (% predicted) decline of 18 patients 1 year before, at the start of, and after 1 year of cyclophosphamide treatment.

Fig. 2. Kaplan-Meier curves of 26 patients with IPF, 6 with LIP, 8 with idiopathic NSIP, 7 with RA-ILD, and 7 with pANCA+ ILD (median survival = 14 months) with time to death as outcome event.

pANCA+ ILD the worst (fig. 2). The median survival was 14 months (standard error, SE, 1.4 months) for pANCA+ ILD. Computing of the median survival for the remaining disease groups was not possible due to better survival in these groups. We did not find a significant influence of BAL cytology data, age, or gender

Fig. 3. Kaplan-Meier curves of 26 patients with IPF (median event-free survival = 18 months), 6 with LIP (median event-free survival = 12 months), 8 with idiopathic NSIP, 7 with RA-ILD (median event-free survival = 12 months), and 7 with pANCA+ ILD (median event-free survival = 11 months) with time to death or disease progression as outcome event.

on survival, e.g. calculated with Cox hazard models (data not shown).

Focusing on progression-free survival, defined as a decline of $\leq -10\%$ of FVC or TLC, the same result was observed (fig. 3): NSIP patients exhibited the best course, and pANCA+ ILD patients the worst. The most striking difference was seen in LIP with marked progression of pulmonary function defect without mortality. After initiation of therapy, the median progression-free survival for IPF was 18 months (SE 6.1 months), for LIP 12 months (SE 6.1 months), for pANCA+ ILD 11 months (SE 2.2 months), and for RA-ILD 12 months (SE 6.5 months). We were not able to calculate the median progression-free survival for patients with NSIP due to the better survival.

Discussion

ILDs are characterised by a progressive lung function decline with limited therapeutic options. Inflammatory ILD usually responds well to immunosuppressant therapy, whereas fibrotic ILD, especially IPF patients, have a markedly reduced median survival of 2–3 years [20, 25–27] due to acute exacerbations and/or progressive loss of lung function. Therefore, the need for evaluation of therapeutic strategies is great and unmet; thus, in this study, we analysed the effect of cyclophosphamide treatment in ILD patients.

In general, i.v. cyclophosphamide was well tolerated by the patients. Yet, one third of the patients did not entirely receive the six planned cyclophosphamide infusions. The main reasons for premature cessation of treatment were infections. Infections are frequent in ILD patients and may be a side effect of cyclophosphamide or a consequence of the ILD itself. Infections under i.v. cyclophosphamide pulse therapy are reported in up to 30% of patients [28]. Summing up the documented infections and the therapy discontinuation out of other reasons, the rate nearly reaches this reported percentage (pooled 24% in this cohort).

In inflammatory ILD, especially in LIP and NSIP, cyclophosphamide is a safe and beneficial therapeutic option with a good survival. In NSIP patients, we observed an excellent survival and stabilisation of the disease. The reason for the discrepancy between good survival and the observed progression of lung functional defects remains unclear in LIP patients. In clinical experience, LIP patients usually benefit from immunosuppressant therapy. Thus, in view of the absent mortality, a continuation of therapy might have prevented the lung function decline. This needs to be studied in future trials.

The natural clinical course of IPF and other fibrotic lung diseases is a progressive lung function decline [29]; therefore, stopping of deterioration of lung function must be seen as a beneficial treatment effect. In our cohort, cyclophosphamide was able to stabilise the lung function of these patients in a considerable way (57.7% in IPF and 42.8% in pANCA+ ILD patients), with better results in IPF than in pANCA+ ILD. The bad outcome of pANCA+ ILD patients was somehow surprising, as patients with other rheumatologic disorders, such as scleroderma, benefit from cyclophosphamide pulse therapy [21]. Yet in our cohort, pANCA+ ILD patients behave similarly to IPF patients. This may be due to the fact that they also show a fibrotic usual interstitial pneumonia (UIP) pattern in CT scans and UIP patterns are associated with a worse prognosis in rheumatologic disorders [30]. Based on these findings and on the positive and promising results of the RAVE [17] and the MAINRITSAN [18], rituximab seems to be a better treatment option for patients with pANCA+ ILD than cyclophosphamide. Furthermore, rituximab offers a better side effects profile in most cases.

Using a retrospective study design, it is not possible to distinguish stabilisations due to the natural course of the disease or due to treatment. Knowing that patients with rapid progressive IPF, which were the prominent IPF subgroup in this study, have most likely a further worsening of lung function, the stabilisation of their lung function is

certainly partly due to cyclophosphamide treatment. Thus, in case of disease progression under therapy with nintedanib or pirfenidone, cyclophosphamide pulse therapy is an option capable of preserving the pulmonary function. Moreover, in a number of countries nintedanib and pirfenidone are only approved for patients fulfilling inclusion criteria of phase III studies leading to approval, leaving patients with advanced disease without therapy. Of the 8 patients in this category with vital capacity under 50%, none had a progression of IPF, whereas 25% died during the follow-up. Therefore, especially in end-stage IPF patients, cyclophosphamide seems to stabilise the lung function. However, patients with IPF and pANCA+ ILD had the worst survival, maybe partly due to the immunosuppression with cyclophosphamide itself: the high rate of infectious side effects might contribute to the observed higher mortality in fibrotic ILDs, as they are more prone to fatal courses due to the structurally preinjured lungs. Therefore, based on the excess mortality in the azathioprine arm of the PANTHER trial [5], immunosuppression in IPF has since then been contraindicated by most clinicians.

The main limitations of this real-life study are its retrospective nature, which is why not all data were available, and the small sample size. Paired lung function values (before and after treatment) were recorded in 18 of 52 patients. As lung function at baseline showed no significant difference between patients with and patients without available paired lung function (data not shown), a possible bias seems to be small between these groups. Further, we excluded patients with <2 cyclophosphamide infusions to avoid situations with an extremely high risk of death (e.g. patients with acute exacerbation of IPF at the intensive care unit, in whom treatment was started as a last resort). Another limitation is the absence of a placebo group. Especially stabilisation or improvement of the lung function, even though it is less likely to occur spontaneously, may be due to the natural course of the disease in the treated patients. Yet another drawback is that we biased our results by excluding patients with severe side effects or disease progression. However, stopping therapy is a mandatory clinical consequence in those situations.

Conclusion

This retrospective analysis of cyclophosphamide treatment shows a stabilisation of lung function in most patients with fibrotic ILDs, yet prospective studies in clearly defined diagnoses are urgently needed. Patients with NSIP had the most stable lung function during follow-up

and patients with pANCA+ ILD suffered the most from disease progression or death. The main side effects were infectious ones, which might bear a potentially high mortality in patients with pre-injured lungs. An important consequence for further interventional studies arising from this study is to establish biomarkers which will predict treatment response.

Acknowledgements

We would like to thank Dr. Vera Baier (Central Pharmacy, University Hospital Freiburg) for providing the delivery orders of cyclophosphamide.

References

- 1 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2011 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002; 165:277–304.
- 2 Fischer A, Lee JS, Cottin V: Interstitial lung disease evaluation: detecting connective tissue disease. *Respiration* 2015;90:177–184.
- 3 Paschalaki KE, Jacob J, Wells AU: Monitoring of lung involvement in rheumatologic disease. *Respiration* 2016;91:89–98.
- 4 Papiris SA, Manali ED, Kolilekas L, Kagouridis K, Maniati M, Borie R, et al: Investigation of lung involvement in connective tissue disorders. *Respiration* 2015;90:2–24.
- 5 Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ: Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012;366:1968–1977.
- 6 Collard HR, Ryu JH, Douglas WW, Schwarz MI, Curran-Everett D, King TE, et al: Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. *Chest* 2004;125:2169–2174.
- 7 Baughman RP, Lower EE: Use of intermittent, intravenous cyclophosphamide for idiopathic pulmonary fibrosis. *Chest* 1992;102:1090–1094.
- 8 Roig V, Herrero A, Arroyo-Cózar M, Vielba D, Juarros S, Macías E: Comparative study between oral azathioprine and intravenous cyclophosphamide pulses in the treatment of idiopathic pulmonary fibrosis (in Spanish). *Arch Bronconeumol* 2010;46:15–19.
- 9 Pereira CAC, Malheiros T, Coletta EM, Ferreira RG, Rubin AS, Otta JS, et al: Survival in idiopathic pulmonary fibrosis-cytotoxic agents compared to corticosteroids. *Respir Med* 2006;100:340–347.
- 10 Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
- 11 Oltmanns U, Kahn N, Palmowski K, Träger A, Wenz H, Heussel CP, et al: Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. *Respiration* 2014;88:199–207.
- 12 Jones MG, Fletcher S, Richeldi L: Idiopathic pulmonary fibrosis: recent trials and current drug therapy. *Respiration* 2013;86:353–363.
- 13 Antoniou KM, Symvoulakis EK, Anyfantakis D, Wells AU: New treatments for idiopathic pulmonary fibrosis: ‘die another day’ if diagnosed early? *Respiration* 2015;90:352.
- 14 Robles-Perez A, Molina-Molina M: Treatment considerations of lung involvement in rheumatologic disease. *Respiration* 2015;90:265–274.
- 15 Marigliano B, Soriano A, Margiotta D, Vadacca M, Afeltra A: Lung involvement in connective tissue diseases: a comprehensive review and a focus on rheumatoid arthritis. *Autoimmun Rev* 2013;12:1076–1084.
- 16 Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al: Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;63(suppl 5):v1–v58.
- 17 Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221–232.
- 18 Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014;371:1771–1780.
- 19 Cha S-I, Fessler MB, Cool CD, Schwarz MI, Brown KK: Lymphoid interstitial pneumonia: clinical features, associations and prognosis. *Eur Respir J* 2006;28:364–369.
- 20 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
- 21 Austin HA, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al: Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; 314:614–619.
- 22 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al: Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
- 23 Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al: Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511–522.
- 24 Prasse A, Georges CG, Biller H, Hamm H, Matthys H, Luttmann W, et al: Th1 cytokine pattern in sarcoidosis is expressed by bronchoalveolar CD4+ and CD8+ T cells. *Clin Exp Immunol* 2000;122:241–248.
- 25 Antoniou KM, Wells AU: Acute exacerbations of idiopathic pulmonary fibrosis. *Respiration* 2013;86:265–274.
- 26 Isshiki T, Sakamoto S, Kinoshita A, Sugino K, Kurosaki A, Homma S: Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study. *Respiration* 2015;89:201–207.
- 27 Leuchte HH, Mernitz P, Baezner C, Baumgartner RA, von Wulffen W, Neurohr C, et al: Self-report daily life activity as a prognostic marker of idiopathic pulmonary fibrosis. *Respiration* 2015;90:460–467.
- 28 Martin F, Lauwerys B, Lefebvre C, Devogelaer JP, Houssiau FA: Side-effects of intravenous cyclophosphamide pulse therapy. *Lupus* 1997;6:254–257.
- 29 Martinez FJ, Safran S, Weycker D, Starko KM, Bradford WZ, King TE Jr, et al: The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005;142:963–967.
- 30 Joo HP, Dong SK, Park IN, Se JJ, Kitaichi M, Nicholson AG, et al: Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *Am J Respir Crit Care Med* 2007;175:705–711.