Cyclosporine as a treatment in acutely exacerbated interstitial pneumonia: does it add value?

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Objective The aim of this study was to evaluate the efficacy of combined therapy of cyclosporine A (CsA) with prednisolone for acutely exacerbated interstitial pneumonia.

Patients and method Forty-eight patients who were diagnosed as having interstitial pneumonia were recruited in the study. These patients experienced clinical worsening as demonstrated by any one of the following within the past year: greater than 10% decrease in the percent predicted forced vital capacity, worsening high-resolution CT scan or clinical worsening of dyspnea at rest or on exertion. CsA was given at a dose range of 2 mg/kg/day in addition to corticosteroids. Patients were assessed at baseline and then at 1, 3, 6, and 9 months for response to therapy and for any adverse effect of the treatment.

Results Patients were divided according to the underlying systemic disease into either patients with idiopathic pulmonary fibrosis (25 patients) or those with underlying collagen vascular diseases (CVDs; 23 patients). Those with underlying CVDs were divided into either UIP/CVDs (five patients) or nonspecific interstitial pneumonia (NSIP/CVDs) (18 patients). Our results showed an overall better response in the NSIP/CVD group of patients. Follow-up parameters in 14 patients with an improved response showed an improved grade of dyspnea, improved partial pressure of oxygen (PaO_2), %forced vital capacity, and diffusing capacity of carbon monoxide ($\%DL_{CO}$); Krebs von den Lungen 6 (KL6) showed a significant decrease after initiation of CsA treatment when compared with baseline. Furthermore, a benefit of adding CsA to the treatment was the ability to reduce the dose of steroids during the course of treatment.

Conclusion CsA combined with corticosteroids may be an efficacious treatment for acutely exacerbated interstitial pneumonia. *Egypt J Broncho* 2014 8:121–127

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Introduction

Recently, cyclosporine A (CsA) has been shown to be efficacious in the treatment of interstitial pneumonia (IP) associated with polymyositis and dermatomyositis (PM/DM), the conditions of which are refractory to corticosteroid therapy [1–3]. However, the efficacy of CsA in idiopathic interstitial pneumonias (IIPs) is still undetermined. CsA primarily inhibits the activation of T lymphocytes by blocking the expression of the genes such as interleukin 2 (IL-2), which are regulated by the nuclear factor of activated T cell transcription factor. In addition, it has been reported that CsA exerts direct effects on macrophages. As T lymphocytes and alveolar macrophages play an important role in the pathogenesis of idiopathic pulmonary fibrosis (IPF), CsA may have potential efficacy as a modulator of the clinical course of IPF. In contrast, suppression of IL-2 by corticosteroid treatment requires interaction with the activator protein-1. These findings suggest that these two agents contribute to the suppression of IL-2 gene expression in an independent as well as additional or synergistic manner [4,5].

Krebs von den Lungen 6 (KL6) is a high-molecular-weight glycoprotein antigen (classified as a MUC1), first described by Kohno *et al*. [6], that in normal lungs is expressed mainly on type II pneumocytes and bronchiolar epithelial cells, but only weakly in basal cells of the terminal bronchiolar epithelium, a small number of middle layer cells of the bronchial epithelium and serous cells of the bronchial gland. In patients with interstitial lung diseases (ILD), KL6 is strongly expressed on alveolar macrophages and the type II pneumocytes that are regenerated over the alveolar basement membrane after the death of type I pneumocytes during the first stage of fibrosing lung injury. The soluble form of KL6 is evaluable in the bronchoalveolar lavage fluid and also noninvasively in the serum, on the basis of its leakage from the alveolar space into the blood due to an enhanced permeability or destruction of the air–blood barrier in the diseased lungs [7].

The usefulness of the KL6 biomarker has been investigated in several Japanese studies, with consistent findings of increased serum levels in various ILDs,

including radiation pneumonitis, collagen vascular disease (CVD) with ILD, and drug-induced lung disease [8]. In terms of the ongoing evaluation of disease activity and gauging the effectiveness of treatment, it has also been reported that the serum level of KL6 in patients with active IIP is significantly higher than it is in those with inactive IIP [9].

Surfactant protein A (SP-A) and surfactant protein D (SP-D), water-soluble members of the C-type lectin superfamily, are produced in the lung primarily by alveolar epithelial type II cells and are important constituents of the innate immunity of the lung. Serum levels of SP-A and SP-D are increased in IPF, but also other pulmonary diseases, probably due to type II pneumocyte hyperplasia and/or epithelial barrier breakdown [10]. Kinder *et al*. [11] found that high levels of SP-A at the time of initial diagnosis was a strong predictor of mortality in a well-defined group of 82 patients with IPF. Furthermore, a model using baseline serum SP-A and SP-D provided a substantial additive predictive value and was superior to a model based on clinical parameters alone.

With this background, the present study was aimed to assess the efficacy of combined therapy of CsA with prednisolone (PSL) in the treatment of patients with acutely exacerbated IP and the usefulness of serum biomarkers in predicting the response to treatment.

Patients and methods

Forty-eight patients admitted in the Tokushima University Hospital who were diagnosed as having IP were recruited during the period from 2008 through 2009.

These patients experienced clinical worsening as demonstrated by any one of the following within the past year: greater than 10% decrease in the percent predicted forced vital capacity (FVC), worsening high-resolution CT chest or worsening dyspnea at rest or on exertion.

Patients excluded were those with severe disease defined as FVC less than 50% of the predicted value at screening, diffusing capacity of carbon monoxide (DL_{CO}) less than 35% of the predicted (corrected for hemoglobin) value at screening and PaO_2 less than 55 mmHg (sea level) at rest on room air. Other medical and laboratory conditions that resulted in exclusion included an evidence of active infection, a history of unstable or deteriorating cardiac or neurologic disease, creatinine greater than 1.5 times the upper limit of normal at screening and hematology outside of specified limits [white blood cells (WBCs) <2500 mm^3 or absolute neutrophil count<1500; platelets <100 000/mm^3 at screening; any of the following liver function test criteria above specified limits: total bilirubin>2.0´upper limit of normal, raised liver enzymes, and albumin <3.0 mg/dl at screening].

Patients were divided into two groups according to the underlying systemic disease.

Group I included patients with IPF (25 patients). All 25 patients in this group had undergone video-assisted thoracoscopic surgery and an underlying histopathological pattern was consistent with usual IPF (UIP/IPF). In the absence surgical lung biopsy, IPF was diagnosed on the basis of ATS/ERS criteria [12].

Major criteria

(1) Exclusion of other known causes of ILD such as certain drug toxicities, environmental exposures, and connective tissue disease (CTD).
(2) Abnormal pulmonary function studies that include evidence of restriction, reduced vital capacity, impaired gas exchange, decreased PaO_2 with rest, or exercise or reduced DL_{CO}.
(3) Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans.
(4) Transbronchial lung biopsy or bronchoalveolar lavage showing no features that support an alternative diagnosis.

Minor criteria

(1) Age more than 50 years.
(2) Insidious onset of otherwise unexplained dyspnea.
(3) Duration of illness of more than 3 months.
(4) Bibasilar, inspiratory crackles 'dry or velcro' type in quality.

Group II included patients with underlying CVDs (23 patients).

Twenty-three patients had undergone video-assisted thoracoscopic surgery, and the underlying histopathological patterns were consistent with either UIP or nonspecific interstitial pneumonia (NSIP) patterns (UIP/CVDs or NSIP/CVDs).

Patients were assessed at baseline and then at 1, 3, 6, and 9 months for their response to therapy and for any adverse effects of the treatment.

All patients were subjected to the following (at baseline and during the follow-up period).

(1) Full history and clinical examination.
    (a) Age.
    (b) Sex.
    (c) Smoking history.

(d) Underlying diagnosed CVD.
(e) Previous and current therapeutic history (corticosteroids, immunosuppressive therapy: dose and duration).
(f) Assessment of dyspnea according to the Modified Medical Research Council scale.
(g) A history of acute exacerbations that required hospitalization or an increased dose of corticosteroids.

Defining an acute exacerbation: [13]

Previous diagnosis of an ILD or compatible radiological findings synchronous with an acute exacerbation.

(1) Deterioration of symptoms of recent onset (exacerbation of dyspnea within 1 month).
(2) Hypoxemia (with or without a decline in PaO_2 or the PaO_2/FiO_2 ratio compared with the pre-exacerbation status).
(3) New ground glass opacities or consolidation superimposed on the previous chronic CT pattern.
(4) Exclusion of other diagnoses (infection, venous thromboembolic disease, congestive heart failure, pneumothorax).

(2) Laboratory investigations.
(a) WBC count.
(b) C-reactive protein.
(c) Kidney function.
(d) Liver function.
(e) Serum biomarkers KL6, SP-A, SP-D, and LDH.

(3) Chest radiograph.
(4) High-resolution CT-scan images were evaluated. Routine scanning of the entire lung was carried out with 10-mm-thick sections. Additional thin-section CT with 1.0-mm-thick sections of the parenchymal abnormalities was performed for all patients.
(5) Pulmonary function tests.

The forced vital capacity, DL_{CO}, and arterial blood gases were measured.

Treatment protocols

Patients recruited in the present study were maintained on corticosteroids (40–45 mg/day) for different periods of time before beginning CsA treatment. The mean duration of pretreatment with prednisone before administration of CsA ranged from 8.5 to 10.3 months in the three groups of patients. Patients showed progressive disease despite corticosteroid therapy or developed exacerbations of IP during their courses.

CsA was given at a dose range of 2 mg/kg/day in addition to corticosteroids. Blood trough levels of CsA were monitored regularly and CSA levels were adjusted to be between 100 and 200 ng/ml.

Adverse effects

Patients were monitored during each visit for adverse events related to CsA treatment. Hepatic, renal, and hematological functions were also monitored.

Criteria for assessment of the response to treatment

On the basis of the criteria of ATS/ERS international consensus on IPF, responses to the treatment for IP were defined as described below.

(1) Improved response to therapy was defined as two or more of the following:
(a) An improvement of symptoms, especially an increase in the exercise capability caused by dyspnea.
(b) Reduction of parenchymal abnormalities as revealed on chest HRCT scan.
(c) Physiological improvement defined by one or more of the following:
(1) A greater than 10% increase in FVC or at least more than 200 ml change.
(2) A 15% increase in DL_{CO} or at least more than 3 ml/min/mmHg.
(3) A greater than 10 mmHg increase in the resting PaO_2 from the previous level.

(2) Unchanged response to therapy was defined as two of the following:
(a) Persistence of parenchymal abnormalities as shown on HRCT chest.
(b) Physiological stability defined by one or more of the following:
(1) Change in FVC not greater than 10% or a 200 ml change.
(2) Change in single-breath DL_{CO} of less than 15% or less than 3 ml/min/mmHg.
(3) An increase in the resting PaO_2 of less than 10 mmHg from the previous level.

(3) A failure to respond to therapy was defined as two or more of the following:
(a) A worsening of symptoms, especially dyspnea, or cough and/or sputum.
(b) An increase in opacities as revealed on chest HRCT scan.
(c) Physiological deterioration was defined by one of more of the following:
(1) A 10% decrease in FVC or more than 200 ml change.
(2) A decrease in DL_{CO} of more than 15% or 3 ml/min/mmHg.
(3) A decrease in the resting PaO_2 of more than 10 mmHg from the previous level.

Results

Clinical and histopathological features of the patients studied

Forty-eight patients were recruited in the present study: all were diagnosed as IP that was either idiopathic or with underlying systemic disease. Table 1 shows clinical and pathological features of the study population.

As shown in the previous table, patients were divided according to the underlying systemic disease into either patients with IPF (25 patients) or those with underlying CVDs (23 patients).

Video-assisted thoracoscopic surgery to obtain lung biopsy was performed in 43 patients for histopathological diagnosis. Twenty patients had a pattern of UIP with unknown etiology (UIP/IPF).

Those with underlying CVDs were divided into either UIP/CVDs (five patients) or NSIP/CVDs (18 patients). Patients in this group were further subdivided into cellular NSIP (C-NSIP) (14 patients) and fibrotic NSIP (F-NSIP) (four patients) after histopathological diagnosis.

In five patients in whom histopathological diagnosis was not performed, a diagnosis of IPF was made according to ATS/ERS major and minor criteria for the diagnosis of IIPs [12]. Baseline data of the patient were determined before the initiation of CsA treatment as shown in Table 2.

The patient's level of dyspnea was classified on a scale of 0–IV as outlined by the modified MRC dyspnea scale. There was no significant difference in the dyspnea score between the three groups of patients. In the UIP/IPF group, the MMRC dyspnea score was 3.54 ± 0.87; in the UIP/CVDs group, it was 3.2 ± 0.78; and in the NSIP/CVDs group, it was 2.8 ± 0.95.

The mean ± SD of PaO_2, FVC, and DL_{CO} were determined for each group, which did not show any significant difference.

In the UIP/IPF group PaO_2 was 55 ± 7.3, %FVC 55.4 ± 4.6, and $\%DL_{CO}$ was 53.6 ± 13.5. In the UIP/CVDs group, PaO_2, %FVC, and $\%DL_{CO}$ were 53.2 ± 5.5, 62.5 ± 6.5, and 54.5 ± 7.6, respectively. In the NSIP/CVDs group, PaO_2 was 55.7 ± 9.5, %FVC 65 ± 10.6, and $\%DL_{CO}$ 52.5 ± 12.43.

Table 1 Clinical and pathological features of the patients studied

Groups	UIP/IPF	UIP/CVDs	NSIP/CVDs
Number of patients (%)	25 (52)	5 (10)	18 (38)
Age (mean ± SD) (years)	69.6 ± 6.2	64 ± 14	57.3 ± 12.9
Sex [*n* (%)]			
Male	15 (60)	3 (60)	5 (28)
Female	10 (40)	2 (40)	13 (72)
Smoking history			
Never	8 (32)	2 (40)	9 (50)
Former	10 (40)	2 (40)	6 (34)
Current	7 (28)	1 (20)	3 (16)
Underlying systemic disease	None	RA: none SLE: 1 PM/DM: 1 Systemic sclerosis: 3	RA: 3 SLE:3 PM/DM: 5 Systemic sclerosis: 7
Histopathological diagnosis (VATS)	20 UIP	5 UIP	18 C-NSIP 14 F-NSIP 4
HRCT chest scan	Honey combing>ground glass opacity	Honey combing>GGO	GGO>honey combing

C-NSIP, cellular nonspecific interstitial pneumonia; CVDs, collagen vascular diseases; F-NSIP, fibrotic nonspecific interstitial pneumonia; GGO, ground glass opacity; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythromatosis; UIP, usual interstitial pneumonia.

Table 2 Baseline data of patients before the initiation of cyclosporine A treatment

Groups	UIP/IPF	UIP/CVDs	NSIP/CVDs	*P*-value
Number of patients	25	5	18	
MMRC dyspnea score	3.54 ± 0.87	3.2 ± 0.78	2.8 ± 0.95	0.368
Pulmonary function				
PaO_2 (mean ± SD)	55 ± 7.3	53.2 ± 5.5	55.75 ± 9.5	0.732
%FVC (mean ± SD)	55.4 ± 4.6	60.5 ± 6.5	65 ± 10.6	0.534
$\%DL_{CO}$ (mean ± SD)	53.6 ± 13.5	54.5 ± 7.6	52.5 ± 12.43	0.758
Serum biomarkers				
KL6 (*N* = 500) (IU/ml)	3250 ± 517.6	1235 ± 335	918 ± 163	0.043*
SP-A (*N* = 43) (ng/ml)	91.5 ± 35.5	62.3 ± 12.53	94 ± 17	0.452
SP-D (*N* = 110) (ng/ml)	249 ± 88.4	148.4 ± 42.5	154.7 ± 30.4	0.975
LDH (*N* = 110–200) (IU/l)	372.9 ± 84.2	330. ± 58.4	268 ± 130.6	0.861
WBCs/ml	7.493 ± 3.450	6.635 ± 1.250	5.528 ± 2.439	0.556
C-reactive protein	0.24 ± 0.16	0.19 ± 0.09	0.23 ± 0.15	0.345

CVDs, collagen vascular diseases; $\%DL_{CO}$, diffusing capacity of carbon monoxide; %FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; KL6, Krebs von den Lungen 6; LDH, lactic dehydogenase; NSIP, nonspecific interstitial pneumonia; PaO_2, partial pressure of oxygen; SP-A, surfactant protein A; SP-D, surfactant protein D; UIP, usual interstitial pneumonia; WBC, white blood cell.

The serum KL6 was measured as a marker of active pneumonitis. Also, SP-A, SP-D, and LDH were determined, and all were increased in comparison with their normal ranges.

The level of KL6 was markedly increased in UIP/IPF patients (3250 ± 517.6) compared with UIP/CVD and NSIP/CVD patients (P = 0.043). In the UIP/CVD group, the values were 1235 ± 335 and 918 ± 263 for those who had NSIP with underlying CVD.

WBCs and C-reactive proteins were measured to exclude active infection. WBCs were within the normal range, being 7.493 ± 3.450 in the UIP/IPF group, 6.635 ± 1.250 in the UIP/CVD group, and 5.528 ± 2.439 in the NSIP/CVD group. C-reactive protein was 0.24 ± 0.16 in UIP/IPF, 0.19 ± 0.09 in UIP/CVD, and 0.23 ± 0.15 in NSIP/CVD patients.

All patients received corticosteroid therapy before initiation of CsA treatment; patients showed disease progression or developed acute exacerbation despite being on corticosteroids. The mean duration of pretreatment with prednisone before administration of CsA ranged from 8.5 to 10.3 months in the three groups of patients, and the dosage of steroids at the initiation of CsA treatment ranged from 40 to 45 mg/day. There was no significant difference between the three groups of patients regarding the duration or the dosage of steroid treatment.

Treatment and follow-up

All patients received CsA combined with corticosteroids. The dose of CsA was 2 mg/kg, and the blood trough level of CsA was monitored to facilitate the adjustment of the CsA dose. The blood trough level was maintained in a range between 100 and 200 ng/ml throughout the course of treatment to avoid undesired side effects of the drug.

According to the criteria of response mentioned in the methodology, the clinical course of patients can be summarized (Table 3) as follows in the three groups of patients:

(1) In the UIP/IPF group, only 8% of the patients showed an improved response, an unchanged or stable course occurred in 28% of the patients and failure to respond to therapy with CsA or deterioration occurred in 16 patients (64%).
(2) In the UIP/CVDs group, 40% of the patients showed an improved response, 20% had a stable course, and 40% deteriorated.
(3) In the NSIP/CVDs group, 55% of the patients improved after adding CsA to steroids, 28% were stable, and 17% showed deterioration in their clinical course. Of the 10 patients who showed an improved response, 90% had C-NSIP and 10% had F-NSIP. Eighty percent of patients with stable response had C-NSIP and 20% had F-NSIP. Three patients showed a deteriorated response, and the underlying histopathology was F-NSIP.

Follow-up parameters in the 14 patients with improved response are shown in Table 4. The dyspnea score improved from 3.5 ± 0.7 to 2.44 ± 0.86, which was maintained up to 9 months after treatment. They also showed an improved PaO_2, %FVC, and $\%DL_{CO}$ (PaO_2 55.6 ± 7.3 before CsA vs. 76.7 ± 5.5 after CsA; %FVC 60 ± 6.5 vs. 79.8 ± 2.5; and $\%DL_{CO}$ 45.6 ± 12.5 vs. 74.5 ± 4.6). As for serum biomarkers, only KL6 showed a significant decrease after initiation of CsA treatment compared with baseline (whereas SP-A, SP-D, and LDH did not show any significant difference after initiation of CsA). KL6 decreased from 1.350 ± 215.6 before CsA treatment to 615 ± 128 after CsA treatment (P = 0.001). A benefit of adding CsA to the treatment was the ability to reduce the dose of steroids during the course of treatment from a dose range of 45.6 ± 10.5 before CsA to 25 ± 8.02 after adding CsA (P = 0.001).

Table 3 Response to cyclosporine A in patients with interstitial pneumonia after 9 months of treatment

Group of patients	UIP/IPF	UIP/CVDs	NSIP/CVDs
Number of patients	25	5	18
Clinical course [*n* (%)]			
Improved	2 (8)	2 (40)	10 (55)C-NSIP 9 (90)F-NSIP 1 (10)
Unchanged (stable)	7 (28)	1 (20)	5(28)C-NSIP 4 (80) F-NSIP 1(20)
Deteriorated	16 (64)	2 (40)	3(17)C-NSIP 0F-NSIP 3(100)

CVDs, collagen vascular diseases; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

Table 4 Follow-up parameters in 14 patients with an improved response to cyclosporine A

Follow-up parameters	CsA (–)	CsA (+)	*P*-value
MMRC dyspnea scale	3.5 ± 0.7	2.44 ± 0.86	0.001*
Pulmonary function (mean ± SD)			
PaO_2	55.6 ± 7.3	76.7 ± 5.5	0.033*
%FVC	60 ± 6.5	79.8 ± 2.5	0.041*
$\%DL_{CO}$	45.6 ± 12.5	74.5 ± 4.6	0.027*
Serum biomarkers			
KL6 (N = 500) (IU/ml)	1,350 ± 215.6	615 ± 128	0.001*
SP-A (N = 43) (ng/ml)	92.5 ± 10.5	85 ± 7.53	0.453
SP-D (N = 110) (ng/ml)	147 ± 42	136 ± 15.5	0.785
LDH (IU/l)	272.9 ± 58.2	268 ± 35.4	0.933
Dose of steroids	45.6 ± 10.5	25 ± 8.02	0.001*

CsA, cyclosporine A; $\%DL_{CO}$, diffusing capacity of carbon monoxide; %FVC, forced vital capacity; KL6, Krebs von den Lungen 6; LDH, lactic dehydogenase; PaO_2, partial pressure of oxygen; SP-A, surfactant protein A; SP-D, surfactant protein D.

Monitoring of adverse events

New symptoms and signs that manifested during the treatment period were documented as possible adverse effects. During each visit, patients were asked specific questions related to side effects of the treatment. Hepatic, renal, and hematologic functions were also monitored.

In general, reactions were mild and well tolerated, and stopping the treatment was unnecessary. Side effects included influenza-like symptoms, nausea, vomiting, tremor, peripheral edema, gingival hyperplasia, hyperglycemia, depression, parathesia, and headache. No evidence was found for hepatotoxicity.

Discussion

CsA primarily inhibits the activation of T lymphocytes by blocking the expression of genes such as IL-2. It also has a competitive inhibitory effect on P-glycoprotein, which is reported to be one of the mechanisms of resistance to corticosteroids. Although recent studies showed that CsA is effective in the treatment of IP associated with PM and DM, the efficacy of CsA in IP with CTD other than PM/DM and in IIPs remains unknown [3].

In the present study, 48 patients diagnosed as IP confirmed by VATS were divided according to the underlying systemic disease into either patients with IPF (25 patients) or those with underlying CVDs (23 patients). All patients received corticosteroids therapy before the initiation of CsA treatment; patients showed disease progression or developed acute exacerbation despite being on corticosteroids. CsA was added at a dose of 2 mg/kg and the response among patients was monitored. An overall better response was noticed among NSIP/CVD patients; 55% of the patients improved after adding CsA to steroids, 28% were stable and 17% showed deterioration in their clinical course. Of the 10 patients who showed an improved response, 90% had C-NSIP and 10% had F-NSIP. 80% of the patients with a stable response had C-NSIP and 20% had F-NSIP. Three patients showed a deteriorated response and the underlying histopathology was F-NSIP. In the UIP/CVD group, 40% of the patients showed an improved response, 20% had a stable course, and 40% deteriorated.

These results were consistent with a study by Homma *et al*. [14], who evaluated CsA in the treatment of patients with steroid-resistant IP. The underlying systemic diseases were IIPs in 19 patients and CVDs in 14. The histopathological patterns and underlying diseases of IP were classified as UIP/IPF in 10 patients, C-NSIP/IIPs in three, F-NSIP/IIPs in five, organizing pneumonia/IIP in one, UIP/CVDs in four, C-NSIP/CVDs in seven, F-NSIP/CVDs in two, and diffuse alveolar damage/CVD in one patient, respectively. They received a low dosage of CsA combined with corticosteroids. The prognoses after treatment with CsA were well correlated with the histopathological patterns. C-NSIP and organizing pneumonia showed better prognoses than F-NSIP, UIP or diffuse alveolar damage. In addition, CVDs had better prognoses than IIPs, when compared on the basis of the same histopathological patterns.

Our results showed only 8% improvement in the UIP/IPF group, an unchanged or a stable course occurred in 28% of the patients and failure to respond to therapy with CsA or deterioration occurred in 16 patients (64%). This was consistent with Alton *et al*. [15], who reported a poor response to CsA after long-term use, although the initial response was favorable: the mean survival time in CsA-treated patients was doubled from 2.5 to 5 months, in comparison with the controls closely matched for disease severity. In contrast, a study by Moolman *et al*. [16] showed that three of five patients responded to CsA and corticosteroids, with an improvement in dyspnea and an increase in the vital capacity 6 months after treatment.

We have shown follow-up parameters in 14 patients with an improved response. The dyspnea score improved from 3.5 ± 0.7 to 2.44 ± 0.86, which was maintained up to 9 months after treatment. They also showed improved PaO_2, %FVC, and $\%DL_{CO}$ (PaO_2 55.6 ± 7.3 before CsA vs. 76.7 ± 5.5 after CsA treatment, %FVC 60 ± 6.5 vs. 79.8 ± 2.5, and $\%DL_{CO}$ 45.6 ± 12.5 vs. 74.5 ± 4.6). A benefit of adding CsA to the treatment was the ability to reduce the dose of steroids during the course of treatment from a dose range of 45.6 ± 10.5 before CsA to 25 ± 8.02 after adding CsA (P = 0.001).

Our previous results are consistent with the results of Watanabe *et al*. [17]: a multilateral evaluation of combined therapy of CsA and PSL treatment of chronic fibrosing IP associated with collagen tissue disease was performed. They treated patients with CTD-IP confirmed by surgical lung biopsy. The patients were given a combined therapy of CsA with PSL 20 mg/day on alternate days for 1 year. The efficacy was assessed by means of a pulmonary function test, the functional exercise capacity, HRQoL, and the severity of dyspnea.

After 1 year of therapy, improvements in FVC (≥10%), DL_{CO} (≥15%), and the 6-min walking distance (≥28 m) were observed in 59.1, 68.2, 63.6, and 68.2% of all patients, respectively. A statistically significant improvement was also observed in the mMRC.

As for serum biomarkers, we showed that KL6 was increased in all groups of patients studied although it was significantly higher in the UIP/IPF group (3250 ± 517.6) compared with the UIP/CVD and the NSIP/CVD groups ($P = 0.043$). In UIP/CVDs it was 1235 ± 335 and 918 ± 263 for those who had NSIP with underlying CVD. Only KL6 showed a significant decrease after initiation of CsA treatment compared with baseline (whereas SP-A, SP-D, and LDH did not show any significant difference after initiation of CsA). KL6 decreased from 1,350 ± 215.6 before CsA treatment to 615 ± 128 after CsA treatment.

Our results are similar to a study by Nakajima *et al*. [9]; they found that the mean serum level of KL6 was significantly higher ($P < 0.0001$) in patients with active IP than in those with inactive IP, and that the serum KL6 levels increased with deterioration in IP, but decreased significantly when IP treatment was successful. Similarly, a study by Yokoyama *et al*. [18] on 14 Japanese patients with rapidly progressive IPF, demonstrated diminishing levels of KL6 in response to steroid pulse therapy and increased survival 6 months after the start of therapy.

In our present study, although improved response was seen in 14 patients and the dose of steroids was reduced without significant side effects, it had several limitations: first, the study included a small number of patients, and secondly, the effectiveness of CsA alone in the exacerbation of IP could not be evaluated in this study because all of the patients had received concomittant corticosteroid therapy; yet it seems reasonable to add CsA to the treatment of acute exacerbation of IP, particularly in those with underlying CVD, to prevent re-exacerbation of the disease during the withdrawal of corticosteroids. The lack of clinical experience with CsA in the treatment of acute exacerbation of IPF warrants caution in its use. Nevertheless, in view of the poor prognosis of this disease, this promising, albeit limited, experience with CsA justifies further trials.

Conclusion

CsA combined with corticosteroids may be an efficacious treatment for acutely exacerbated IP.

Acknowledgements

Conflicts of interest

None declared.

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