Short Communication

Acute exacerbation of interstitial lung diseases secondary to systemic rheumatic diseases: a prospective study and review of the literature

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Abstract: Acute exacerbation (AE) is a possible manifestation of interstitial lung diseases (ILD) associated to very high mortality. It's defined as clinically significant respiratory deterioration with evidence of new widespread alveolar abnormalities on computed tomography scan. AE is better described in idiopathic pulmonary fibrosis (IPF) but also reported in ILD secondary to connective tissue diseases (CTD) and vasculitis. The main features and the real clinical impact of this severe complication in these patients are not well defined. Aim of our study was to prospectively investigate the incidence, clinical features and outcome of AE in a population of patients with ILD related to CTD and vasculitis. We consecutively enrolled all patients, with ILD secondary to rheumatic systemic diseases, referring to our multidisciplinary outpatient clinic for rare lung diseases. All patients were followed for at least 12 months (range, 12–36 months). At baseline, all patients underwent to a core set of laboratory investigations and periodically followed; data about demographic, disease onset, clinical, serological and therapeutic features were also recorded. AE occurred in 9/78 patients, with an incidence of 5.77/100 patients/year, and 5/9 patients died because of AE. The baseline value of DLCO was significantly associated to the risk of AE at Cox regression. In patients with ILD related to rheumatic systemic diseases AE can occur with an incidence similar to IPF. Rheumatologists should carefully consider this life-threatening complication as a possible natural course of all patients with ILD secondary to systemic rheumatic disease.

Keywords: Connective tissue diseases (CTDs); rheumatoid arthritis (RA); interstitial lung disease (ILD); lung fibrosis; acute exacerbation (AE)

Submitted Sep 30, 2018. Accepted for publication Mar 09, 2019.
doi: 10.21037/jtd.2019.03.28
View this article at: http://dx.doi.org/10.21037/jtd.2019.03.28

Introduction

Interstitial lung disease (ILD) represents one of the most frequent complication of many systemic autoimmune rheumatic diseases, mainly rheumatoid arthritis (RA), connective tissue diseases (CTDs), and more rarely vasculitides. The clinical course of ILD secondary to CTD or vasculitis is variable, ranging from a slow progressive decline of lung function over time to a rapidly progressive course (1).

Some patients with ILD experience an acute idiopathic

respiratory deterioration called acute exacerbation (AE) associated to very high mortality (2) and described for the first time in patients with idiopathic pulmonary fibrosis (IPF) (3). AE has also been reported in various forms of ILD other than IPF, included ILD secondary to systemic autoimmune rheumatic diseases (4-9).

However, the number of reported cases of AE in CTD-ILD and vasculitis-ILD is very small, and available literature data doesn't clarify the real clinical impact of this severe complication in CTD patients (10).

Aim of our study was to prospectively investigate incidence, clinical features and outcome of AE in a population of patients with ILD secondary to systemic inflammatory rheumatic diseases, namely CTD, RA, and vasculitis.

Patients and methods

During a 24 month-period (January 1st, 2014–December 31st, 2015), we enrolled in a cross-sectional study all consecutive patients affected by ILD secondary to systemic autoimmune rheumatic diseases, both incident and prevalent cases, referring to our clinic dedicated to rare lung diseases (11-14). All patients were evaluated by a multidisciplinary team, composed by rheumatologist, pulmonologist and radiologist, with a long-term experience on clinical aspects and treatment of both ILDs and rheumatic diseases. The study was approved by the local ethical committee and all patients signed a consent form before to enter in the study.

Assessment of rheumatic disease

At baseline, all patients underwent to a core set of serum autoantibodies and laboratory investigations; data about demographic, disease onset, clinical, serological and therapeutic features were also recorded. The initial patient's assessment was followed by a periodical re-evaluation until December 31, 2016. If AE occurred, its clinical course and outcome were also reported.

Rheumatic diseases were classified according to the current international classification criteria: in particular, Systemic sclerosis (SSc) according to 2013 Classification Criteria (11), Sjogren syndrome (SS) according to 2002 or 2016 ACR/EULAR Sjögren's Syndrome Classification Criteria (12), inflammatory muscle diseases were classified according to Bohan and Peter criteria (13), and RA was classified according to 2010 ACR/EULAR RA Classification Criteria (14). For the ANCA associated vasculitides we used the 1990 Criteria for Churg-Strauss Syndrome (formerly eosinophilia with Granulomatosis with Polyangiitis) and Wegener granulomatosis (formerly Granulomatosis with Polyangiitis) (15,16). Finally, the preliminary research criteria for the "interstitial pneumonia with autoimmune features" (IPAF) were used to classify patients who have ILD with autoimmune features, but not fulfill the specific criteria for CTD (17).

Assessment of lung involvement

Diagnosis of ILD was made by mean of high-resolution computed tomography (HRCT). All images were scored by a thoracic radiologist experienced in ILD, classifying them as definite, possible or inconsistent with usual interstitial pneumonia (UIP) pattern (1). If an inconsistent with UIP pattern was noted, the pattern was furtherly classified in nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), mixed pattern NSIP/OP or lymphoid interstitial pneumonia (18), classifying patients according to the prevalent pattern. The result of pulmonary function tests was expressed as the percentage of the predicted value of each parameter and corrected for age, gender and height. Single-breath diffusing capacity of the lung for carbon monoxide (DLCO) was used to assess gas transfer. Clinical evaluation and pulmonary function tests were repeated every 3 months or when a deterioration of clinical status occurred.

Diagnosis of AE

In absence of dedicated diagnostic criteria for AE in ILD related to rheumatic disorders, we adopted the revised diagnostic criteria for AE-IPF (3): acute worsening or development of dyspnea typically of less than 1-month duration; HRCT with new bilateral ground-glass opacities and/or consolidations superimposed on a background pattern consistent with UIP pattern; deterioration not fully explained by cardiac failure or fluid overload. As previously suggested, the occurrence of this clinical and radiological picture in a background of possible or inconsistent with UIP pattern was also considered diagnostic for AE (10). When clinically suggestive, blood β-D glucan and cytomegalovirus antigen were also searched, while quantiferon test was performed in all patients.

When possible, for all patients, bronchoscopy with washings or bronchoalveolar lavage (BAL) was performed to exclude infections. C-reactive protein, blood cultures and

sputum cultures were also performed in all patients.

Statistical analysis

Categorical variables were analyzed by chi square test or Fisher's exact test and differences between the means were determined using Mann-Whitney test for unpaired samples. Clinical features were considered as dichotomic or ordinal parameters (HRCT patterns, sex, antinuclear antibodies, smoke); for DLCO and forced vital capacity (FVC) a cut-off of 47% and 75% was identified according to previous data (16). Finally, age, durations of rheumatic disease and ILD were considered as continuous values. P values<0.05 were considered statistically significant. To define the possible predictive factors of AE only baseline values were considered. Cox regression was performed to analyze the effect of the baseline features of the patients on development of AE and survival and cumulative survival rates were computed by the Kaplan-Meier method (19).

Results

Seventy-eight patients with ILD associated to systemic autoimmune disease (mean age 65.7±11.4, female/male 51/27) were enrolled in the study, and observed for a mean follow-up period of 23.9±10.9 months (range, 12–36 months) (*Table 1*).

Diagnosis of ILD was contemporary to the rheumatic disease in 18/78 (23.1%) patients; ILD preceded the diagnosis of the rheumatic disease in 29/78 (37.2%) subjects, while in the remaining 31 (39.7%) patients ILD occurred during the course of the rheumatic disease. At baseline, the mean duration of rheumatic disease and ILD was 52.5±75.4 and 25.8±35.3 months, respectively.

A definite or possible UIP pattern was observed in 48.7% of cases, while an inconsistent with UIP pattern was recorded in 51.3%. Antinuclear antibodies (ANA) were positive in 67.9% of subjects and extractable nuclear antigens in 41.1%, mainly anti-SSA antibodies (*Table 1*).

Finally, 57 patients (73.1%) underwent immunosuppressive drugs, while steroids were administered in 70 patients (89.8%), prevalently at low dosage (prednisolone ≤5 mg daily).

Patients with AE

Nine patients experienced an AE, with an estimated incidence of 5.77 AE/100 patients/year. In a patient, a relapse of AE was observed 4 months after the first episode. On average, AE appeared 73±76.6 months after diagnosis of CTD or vasculitis and 41.7±28.9 months after diagnosis of ILD. Clinical and serological features of patients with AE are described in *Table 2*. Triggering factors such as infections were excluded in all patients by mean of serology and BAL and no patients had a recent history of infection. Cytological analysis of BAL fluid revealed non-specific presence of low levels of neutrophils and lymphocytes, thus reinforcing the exclusion of infection. When performed blood β-D glucan and cytomegalovirus antigen were negative, as well as quantiferon test. Moreover, none of the patients that experienced AE showed a BAL fluid compatible with alveolar hemorrhage. None of the patient experienced further deterioration of respiratory failure after BAL had been performed. Only in one patient (patient 2, *Table 2*) the AE could be triggered by a lung biopsy. At baseline, DLCO was lower in patients developing AE (46.8±17.9 *vs.* 34.5±10.2, respectively; P not significant); however, a DLCO <47% was recorded in all patients with AE versus 52.2% of the patients without AE (P=0.018). A definite or possible UIP pattern was observed in 6/9 AE cases, while 2 patients showed a NSIP pattern and one a mixed NSIP/OP pattern (not significant); No other significant differences were observed between patients with or without AE, including the frequency of previous use of immunosuppressive drugs or steroids and the type of rheumatic disease (*Table 1*). The baseline value of DLCO was the only factor associated to the development of AE at univariate analysis, also confirmed at multivariate Cox regression, with 1.057-fold reduction of the risk for every 1%-increase of DLCO (HR: 0.946; 95% CI, 0.897–0.997; P=0.037).

Outcome

All patients with AE were hospitalized in a Respiratory Intensive Care Unit and treated with high dose steroids (6-metyl-prednisone 500 mg daily for 3 days, followed by 1 mg/kg daily), O_2 therapy and life-support treatment (3,8).

Four patients died within 1 month by AE; one patient died 4 months after the first episode of AE because of a relapse, despite anti-CD20 therapy. Two of three survived patients recovered their previous lung function, while the third patient showed a significant reduction of lung function after AE.

Overall, 12 patients died during the follow-up, and AE was the main cause of death in 5 patients; 3 other subjects died for infections, 2 for the evolution of the lung disease,

Table 1 Features of the patients enrolled in the study

Features	Total, N=78	AE, N=9	no AE, N=69	P
Sex, M/F	27/51	3/6	24/45	0.94
Smokers	34 (43.6)	1 (11.1)	33 (47.8)	0.22
Age at beginning of FU (yrs)	65.7±11.4	70.0±8.8	65.1±11.6	0.67
Age diagnosis ILD (yrs)	63.4±11.6	67.8±8.5	62.8±11.9	0.41
Age diagnosis RD (yrs)	61.2±12.6	65.1±11.4	60.7±12.7	0.48
HRCT pattern				0.66
Definite/possible UIP	38 (48.7)	6 (66.6)	32 (46.4)	
Inconsistent with UIP	40 (51.3)	3 (33.3)	37 (53.6)	
NSIP pattern	25 (32.1)	2 (22.2)	23 (33.3)	
NSIP/OP pattern	14 (17.9)	1 (11.1)	13 (18.8)	
LIP pattern	1 (1.3)	0	1 (1.4)	
Rheumatic disease				
Rheumatoid arthritis	19 (24.4)	2 (22.2)	17 (24.6)	0.88
UCTD	17 (21.8)	3 (33.3)	14 (20.3)	0.75
Sjogren syndrome	16 (20.5)	0	16 (23.2)	0.13
Systemic sclerosis	11 (14.1)	1 (11.1)	10 (14.5)	0.86
ANCA associated vasculitis	7 (9.0)	1 (11.1)	6 (8.7)	0.75
Inflammatory muscle diseases	5 (6.4)	0	5 (7.2)	0.12
Mixed connective tissue disease	2 (2.6)	1 (11.1)	1 (1.4)	0.18
Overlap SSc-DM	1 (1.3)	1 (11.1)	0	0.10
Antinuclear antibodies	53 (67.9)	6 (66.7)	47 (68.1)	0.66
Anti-ENA	32 (41.0)	4 (44.4)	28 (40.6)	0.68
Anti-SSA	18 (23.1)	1 (11.1)	17 (24.6)	0.63
Anti-SSB	6 (7.7)	1 (11.1)	5 (7.2)	0.81
Anti-CENP-B	5 (6.4)	0	5 (7.2)	0.75
Anti-Scl70	4 (5.1)	1 (11.1)	3 (4.3)	0.63
Anti-U1RNP	3 (3.9)	1 (11.1)	2 (2.9)	0.81
Anti-PM/Scl	2 (2.6)	1 (11.1)	1 (1.4)	0.58
Anti-Jo1	2 (2.6)	0	2 (2.9)	0.56
Anti-PL7	1 (1.3)	0	1 (1.4)	0.87
Anti-neutrophil cytoplasmic antibodies	4 (5.1)	1 (11.1)	3 (4.3)	0.23
Rheumatoid factor	19 (24.7)	2 (22.2)	17 (24.6)	0.63
Anti-citrullinated peptides antibodies	10 (12.8)	0	10 (14.5)	0.12
Forced vital capacity (%)	80.2±22.1	72.9±21.2	80.5±22.3	0.062
DLCO (%)	45.9±17.9	34.5±10.2	46.8±17.9	0.071
Immunosuppressive drugs	57 (73.1)	9 (100.0)	48 (69.6)	0.18
Steroids	70 (89.7)	9 (100.0)	61 (88.4)	0.39

Where is not otherwise specified data are expressed as number (percentage). AE, acute exacerbation; M, male; F, female; FU, follow-up; ILD, interstitial lung disease; RD, rheumatic disease; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia; OP, organizing pneumonia; NSIP, nonspecific interstitial pneumonia; UCTD, undifferentiated connective tissue disease; ANCA, anti-neutrophil cytoplasmic antibodies; SSc-DM, systemic sclerosis/dermatomyositis (SSc/DM) overlap; ENA, extractable nuclear antigens; Anti-SSA, anti-Sjögren's-syndrome-related antigen A; anti-SSB, anti-Sjögren's-syndrome-related antigen B; anti-CENP-B, anti-centromere autoantigen B; anti-Scl70, anti-topoisomerase I antibody; anti-U1RNP, anti-U1Ribonuclear protein antibody; anti-PM/Scl, anti-polymyositis-scleroderma antibody; anti-Jo1, Histidyl-tRNA synthetase antibody; anti-PL7, anti-threonyl-tRNA synthetase antibody; DLCO, single-breath diffusing capacity of the lung for carbon monoxide.

Table 2 Clinical features of patients with acute exacerbation

Case, age	Rheumatic disease	Age at ILD diagnosis	HRCT pattern	Lung function	Autoantibodies	Features of CTD	Ongoing treatment at AE occurrence	Interval between ILD and AE (months)	P/F ration at the time of AE onset	Treatment/ outcome
1. Male, 70, nonsmoker	SSc	68	NSIP	FVC 75%, DLCO 40%	Anti-Scl70	Sicca syndrome Raynaud's phen.	CFX (12 months), cumulative dose 20 gr (until 18 months before AE)	30	230	High dose steroids/alive, deterioration of lung capacity
2. Male, 75, nonsmoker	ANCA associated vasculitis	73	Definite UIP	FVC 83%, DLCO 33%	p-ANCA	Axonal demyelinating neuropathy	CFX (6 months), cumulative dose 11.5 gr (until first AE)	18	180	High dose steroids/death
3. Female, 80, nonsmoker	pSS	72	Definite UIP	FVC 98%, DLCO 35.3%	Anti-SSA, anti-SSB	Raynaud's phen. Oral dryness	CFX (12 months), cumulative dose 14 gr (until 5 years before AE)	102	166	High dose steroids/death
4. Female, 73, nonsmoker	Overlap SSc-DM	69	Possible UIP	FVC 61%, DLCO 17%	Anti-PM/Scl	Myositis, oligoarthritis skin sclerosis, Esophageal acalasy, Raynaud's phen., scleroderma pattern at NVC	CFX (9 months), cumulative dose 5 gr (until AE)	50	149	High dose steroids/alive
5. Female, 68, nonsmoker	IPAF	65	NSIP	FVC 67%, DLCO 39%	ANA homogeneous titre 1/320	Sicca syndrome Raynaud's phen	CFX (cumulative dose 5 gr until AE)	48	204	High dose steroids/death
6. Female, 74, nonsmoker	RA, Secondary SS	68	NSIP/OP	FVC 94.8%, DLCO 45%	ANA, Ra test, APCA negative	Sicca syndrome, erosive polyarthritis	Methotrexate (6 years)	13	213	High dose steroids/alive
7. Female, 53, nonsmoker	MCTD	52	Definite UIP	FVC 39%, DLCO 22%	Anti-U1RNP	Polyarthritis, puffy hands, Raynaud's phen., sicca syndrome	MMF (3 months)	15	137	High dose steroids/alive
8. Female, 53, nonsmoker	RA	83	Definite UIP	FVC 58%, DLCO 43%	–	Polyarthritis	Etanercept (5 months)	6	181	High dose steroids/death
9. Male, 64, smoker	IPAF	61	Definite UIP	FVC 102%, DLCO 46.5%	Rheumatoid factor	Olygoarthritis, sicca syndrome	Azatioprine (3 months) MMF (6 months)	42	89	High dose steroids/death

ILD, interstitial lung disease; HRCT, high resolution computed tomography; CTD, connective tissue disease; AE, acute exacerbation; SSc, systemic sclerosis; ANCA, anti-neutrophil cytoplasmic antibodies; UCTD, undifferentiated connective tissue disease; RA, rheumatoid arthritis; pSS, Sjogren syndrome; MCTD, mixed connective tissue disease; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; FVC, forced vital capacity; DLCO, single breath-diffusing capacity of the lung for carbon monoxide; Anti-Scl70, anti-topoisomerase I Antibody; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; Anti-SSA, Anti-Sjögren's-syndrome-related antigen A; Anti-SSB, anti-Sjögren's-syndrome-related antigen B; Anti-PM/Scl, Anti-polymyositis-scleroderma Antibody; ANA, anti-nuclear antibodies; Ra test, Reuma test; APCA, anti-citrullinated protein antibodies; anti-U1RNP, anti-U1Ribonuclear protein antibody; NVC, nailfold video capillaroscopy; CFX, cyclophosphamide; MMF, mycophenolate mofetil; P/F ratio, PaO_2/FiO_2 ratio.

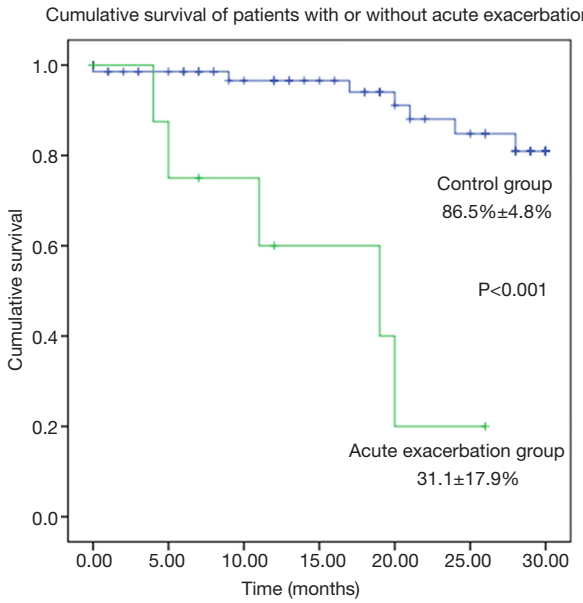

Figure 1 Kaplan-Meyer representation of cumulative survival of ILD patients with or without acute exacerbation (AE). Patients with AE showed a significantly lower survival of patients without AE (31.1%±17.9% *vs.* 86.5%±4.8%, respectively; P<0.001).

the last 2 for the complications of a lung transplantation and for aspiration pneumonia. Survival of patients with and without AE was summarized in *Figure 1*. The baseline value of DLCO was the only predictive factor of death with a reduction of the risk of 0.946 for every 1%-increase of DLCO (HR: 0.951; 95% CI, 0.911–0.992; P=0.02).

A baseline valued of DLCO <47% was associated to a 9.77-fold increase of the risk of death (95% CI, 1.57–60.97).

Finally, the patient 9 died in January 2017, one month after an AE occurred in December 2016 (*Table 2*).

Discussion

Our study aimed to investigate prospectively the incidence, clinical features and outcome of AE in a population of ILD related to CTD (including RA) and vasculitis.

AE is a severe complication of interstitial pneumonia, mainly described in IPF patients with a heterogeneous incidence rate (3,4,20-22). A recent meta-analysis of 6 clinical trials revealed a weighted average of 41 AE per 1,000 patients/year in IPF patients, showing a higher incidence in cohort studies than in clinical trials, from 86 to 142 per 1,000 patients-years (23). AE deeply influences the prognosis of the patients with IPF and up to 46% of deaths in IPF are preceded by an AE (23).

More recently, the occurrence of AE was recorded in other forms of interstitial pneumonia than IPF, but nowadays, less than 50 cases of AE of ILD associated to autoimmune systemic rheumatic diseases have been retrospectively described (*Table 3*; 4-9,23).

In 2003, Rice *et al.* described for the first time 8 cases of AE in CTD (4). Subsequently, a case series of 9 consecutive patients with CTD and histologically proved diffuse alveolar damage was described, reinforcing the hypothesis that AE can complicate the clinical course of patients with CTD-related ILD (5).

In 2007, Park *et al.* reported 4/93 AE occurred in patients with CTD-ILD with a frequency of 3.3% per year; in two cases the AE occurred after surgical biopsy and all patients died (6). Similarly, in 2009 Suda reported the death of 5/6 patients with AE in a cohort of 83 CTD-ILD (7).

Toyoda *et al.* retrospectively described 56 cases of acute deterioration of respiratory conditions in 155 CTD-ILD patients, and 10 of them were diagnosed as affected by AE with a prevalence of 6.5%; only one patient died (8).

Recently, several retrospective case series have described the association of ILD and anti-neutrophil cytoplasm antibodies (ANCA) associated vasculitis (AAV), particularly anti-myeloperoxidase ANCA (24). In the majority of these patients, pulmonary fibrosis occurs concurrently or precedes the diagnosis of AAV (25) The clinical history of ILD in these patients didn't differ by that described in other forms of secondary ILD. At our knowledge, our patient number 2 is the second case of AE described in ILD secondary to AAV (26).

Our study showed an estimated incidence of AE of 5.77 AE/100 patients/year and this data was in line with that reported for IPF patients (3,21-23), but larger studies need to confirm these data. In our population, AE was more frequently observed in patients with UIP pattern, but also detectable in patients with different radiologic patterns (p not significant).

In the present study, AE has proved to be a life-threatening complication and, as previously described in IPF, it represents the first cause of death, followed by infective complications (3,25).

Of course, this paper presents some limits, mainly the short period of observation, the low number of patients, and the heterogeneity of the enrolled group.

Diagnosis of AE of ILD in the context of rheumatic disease is quite difficult in clinical practice. Many confusing factors have to be considered, such as opportunistic infections. To avoid misdiagnosis, all patients with AE in

Table 3 Acute exacerbation of interstitial lung disease in patients with systemic autoimmune rheumatic diseases: review of the literature

Year	Author	Ref	Number of cases	Type of study	Radiological or histological pattern	Outcome	Incidence
2003	Rice AJ	4	8 (2 DM, 2 SSc, 2 SLE, 1 RA, 1 Still)	Autopsy Study; retrospective	3 NSIP, 5 none[§]	8/8 patients died*	NA
2006	Parambil JG	5	9 (5 AR, 2 PM, 1 SSc, 1 MCTD)	Biopsy study; retrospective	2 UIP, 1 NSIP, 3 OP, 3 none[§]	5/9 patients died	NA
2007	Park IN	6	4 (3 RA, 1 SSc)	Cohort study; retrospective	3 UIP, 1 NSIP	4/4 patients died	1-year frequency, 3.3%
2009	Suda T	7	6 (5 RA, 1 pSS)	Biopsy study; retrospective	3 UIP, 2 NSIP, 1 unclassifiable	5/6 patients died	1-year incidence, 1.25%
2016	Toyoda Y	8	10 (6 RA, 2 PM/DM, 1 SLE, 1 pSS)	Cohort study; retrospective	8 UIP, 2 NSIP	1/10 patients died	overall incidence, 6.5%
2007	Silva CI	9	8 (3 RA, 4 DM, 1 pSS)	Biopsy study; retrospective	5 UIP, 3 NSIP	6/8 patients died	NA
2013	Ando M	24	3 (2 UCTD, 1 AAV)	Cohort study; retrospective	3 UIP	3 patients died	NA
Present series	Manfredi A	–	9 (2 RA, 2 UCTD, 2 SSc, 1 MCTD, 1 AAV, 1 pSS)	Cohort study; prospective	6 UIP, 2 NSIP, 1 OP	5/9 patients died	1-year incidence, 5.77%

[§], in 8 patients there was no evidence of interstitial pneumonia before acute exacerbation; *, the study reviewed only deceased patients; DM, dermatomyositis; PM, polymyositis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; Still, adult Still disease; Pss, primary Sjögren's syndrome; UCTD, undifferentiated connective tissue disease; MCTD, mixed connective tissue disease; AAV, associated vasculitis; NA, not available.

our study underwent BAL to exclude infections.

Further large studies could better clarify possible predictive risks of AE in patients with CTDs, RA, and vasculitides, and evaluate possible differences among the single rheumatic diseases. Our data suggest to carefully considering this life-threatening complication as a possible natural course of ILD secondary to rheumatic inflammatory disease, such as for IPF patients. This could allow an early diagnosis and a prompt management, in particular in patients with lower DLCO.

Acknowledgements

A grant of 60.000 Euro from FAR (Fondo di Ateneo per la Ricerca) by University of Modena and Reggio Emilia has allowed the study.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Raghu G, Collard HR, Egan JJ, 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.
2. Tachikawa R, Tomii K, Ueda H, et al. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related versus idiopathic. Respiration 2012;83:20-7.
3. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med 2016;194:265-75.
4. Rice AJ, Wells AU, Bouros D, et al. Terminal diffuse alveolar damage in relation to interstitial pneumonias. An autopsy study. Am J Clin Pathol 2003;119:709-14.
5. Parambil JG, Myers JL, Ryu JH. Diffuse alveolar damage: uncommon manifestation of pulmonary involvement in patients with connective tissue diseases. Chest 2006;130:553-8.
6. Park IN, Kim DS, Shim TS, et al. Acute exacerbation of

interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest 2007;132:214-20.
7. Suda T, Kaida Y, Nakamura Y, et al. Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. Respir Med 2009;103:846-53.
8. Toyoda Y, Hanibuchi M, Kishi J, et al. Clinical features and outcome of acute exacerbation of interstitial pneumonia associated with connective tissue disease. J Med Invest 2016;63:294-9.
9. Silva CI, Müller NL, Fujimoto K, et al. Acute exacerbation of chronic interstitial pneumonia: high-resolution computed tomography and pathologic findings. J Thorac Imaging 2007;22:221-9.
10. Papanikolaou IC, Drakopanagiotakis F, Polychronopoulos VS. Acute exacerbations of interstitial lung diseases. Curr Opin Pulm Med 2010;16:480-6.
11. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737-47.
12. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European consensus group. Ann Rheum Dis 2002;61:554-8.
13. BohanA, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344-7.
14. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
15. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.
16. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
17. Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 2015;46:976-87.
18. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697-722.
19. Altman DG. Practical statistic for Medical Research. London: Chapman & Hall al; 1991.
20. Mura M, Porretta MA, Bargagli E, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J 2012;40:101-9.
21. Luppi F, Cerri S, Taddei S, et al. Acute exacerbation of idiopathic pulmonary fibrosis: a clinical review. Intern Emerg Med 2015;10:401-11.
22. Atkins CP, Loke YK, Wilson AM. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. Respir Med 2014;108:376-87.
23. Kondoh Y, Taniguchi H, Kawabata Y, et al. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest 1993;103:1808-12.
24. Ando M, Miyazaki E, Ishii T, et al. Incidence of myeloperoxidase anti-neutrophil cytoplasmic antibody positivity and microscopic polyangitis in the course of idiopathic pulmonary fibrosis. Respir Med 2013;107:608-15.
25. Kondoh Y, Taniguchi H, Katsuta T, et al. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2010;27:103-10.
26. Alba MA, Flores-Suárez LF, Henderson AG, et al. Interstital lung disease in ANCA vasculitis. Autoimmun Rev 2017;16:722-9.

Cite this article as: Manfredi A, Sebastiani M, Cerri S, Vacchi C, Tonelli R, Della Casa G, Cassone G, Spinella A, Fabrizio P, Luppi F, Salvarani C. Acute exacerbation of interstitial lung diseases secondary to systemic rheumatic diseases: a prospective study and review of the literature. J Thorac Dis 2019;11(4):1621-1628. doi: 10.21037/jtd.2019.03.28

