SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2021; 38 (1); e2021002 DOI: 10.36141/svdld.v38i1.11271

Cyclophosphamide for the treatment of Acute Exacerbation of Interstitial Lung Disease: A Review of the Literature

Ayoub Innabi, Diana Gomez-Manjarres, Bashar N. Alzghoul, Mwelwa Chizinga, Borna Mehrad, Divya C. Patel

Division of Pulmonary, Critical Care and Sleep Medicine; University of Florida; Gainesville, FL

Abstract. Acute exacerbation of interstitial lung disease is a serious and life-threatening event but little is known about its treatment. Cyclophosphamide has been proposed in randomized clinic trials as a treatment option in progressive cases of systemic sclerosis related interstitial lung disease. However, in acute exacerbation of interstitial lung disease, we found only small case series, and retrospective studies, mostly with no comparative groups which described the role of cyclophosphamide. Results of these studies showed mixed outcomes, with no robust evidence that cyclophosphamide adds any benefit in treating acute exacerbations of interstitial lung disease. More well-designed studies including randomized clinical trials are needed to better understand the role of cyclophosphamide during exacerbations of interstitial lung disease. In this review article, we summarize the current evidence on the use of cyclophosphamide in interstitial lung disease with a focus on the acute exacerbation events.

Key words: Cyclophosphamide, Interstitial Lung Disease, Acute Exacerbation

Abbreviations:
AE-ILD: acute exacerbation of interstitial lung disease
AE-IPF: acute exacerbation of idiopathic pulmonary fibrosis
AZA: azathioprine
CT: computed tomography
CTD-ILD: connective tissue disease-interstitial lung disease
CyA: cyclosporin A
CYC: cyclophosphamide
FAST: Fibrosing Alveolitis in Scleroderma Trial
FEV1: forced expiratory volume in one second
FVC: forced vital capacity
DLco: Diffusion capacity of carbon monoxide
HRCT: high resolution computed tomography
ILD: interstitial lung disease
IPF: idiopathic pulmonary fibrosis
MMF: mycophenolate mofetil
PaO_2/FIO_2: partial pressure of arterial oxygen to the fraction of inspired oxygen ratio
RA-ILD: rheumatoid arthritis interstitial lung disease
SLS I: Scleroderma Lung Study I
SLS II: Scleroderma Lung Study II
SSc-ILD: systemic sclerosis-interstitial lung disease

Received: 26 January 2021
Accepted after revision: 30 March 2021

Correspondence: PD Ayoub Innabi
1600 SW Archer Road
Gainesville, FL 32610
Tel.: +1 352-273-8734
E-mail:ayoub.innabi@medicine.ufl.edu

Introduction

Acute exacerbation of interstitial lung disease (AE-ILD) is a serious life-threatening event, with a reported median post-acute exacerbation survival of only 3-4 months (1, 2). In patients with idiopathic

pulmonary fibrosis (IPF), acute exacerbations reduce survival and are the most common cause of death on autopsy. In large series of 461 patients with IPF, Song *et al*, reported that those who experienced acute exacerbations had in-hospital mortality rate of 50%, and the 1- and 5-yr survival rates from the initial diagnosis were 56% and 18%, respectively (3). In connective tissue disease-interstitial lung disease (CTD-ILD), a review of 155 patients found that the 10 patients who experienced acute exacerbation had a median survival of only 169 days after acute exacerbation (4).

Although the prognosis of AE-ILD disease is poor, treatment is unknown. Immunosuppressing agents such as cyclophosphamide (CYC) have been proposed as treatment option in the literature (5, 6). We sought to review the literature on the role of CYC in AE-ILD after reviewing how it is typically used in chronic ILD.

Methodology

An electronic search was implemented in PubMed, Google Scholar and Medline. Search terms included the term "cyclophosphamide", "exacerbation", "idiopathic pulmonary fibrosis", "lung fibrosis", "interstitial lung disease" and/or "connective tissue disease". Publications were only included in the review if they were written in English or the abstract was in English. No date limits were set. From the articles retrieved in the first search round, the search strategy was amplified by manual screening of the reference lists of identified studies. As the review is narrative and not systematic, the references were selected according to the relevance to the subject of the review.

Overview of Acute Interstitial Lung Disease Exacerbation

Currently, acute exacerbation is only defined in IPF, however similar criteria are often used to define acute exacerbation in other ILDs (1, 7). Definition and criteria for AE-IPF were published in 2007 and revised in 2016 by an international working group, which defined AE-IPF as an "acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality,". The 2016 International Working Group Report proposed the following diagnostic criteria for AE-IPF: (a) previous or concurrent diagnosis of IPF; (b) acute worsening or development of dyspnea typically less than one month in duration; (c) presence of new bilateral ground-glass opacities and/or consolidations superimposed on a background pattern of UIP on high resolution computed tomography (HRCT) scans; and (d) clinical deterioration not fully explained by heart failure or fluid overload (1, 8, 9). The 2007 criteria for diagnosis of AE-IPF were strict, requiring careful exclusion of pulmonary infection, left heart failure, pulmonary embolism, and identifiable causes of acute lung injury (9). However, some of these causes, including infection and drug toxicity, were allowed as triggers of acute exacerbation in the 2016 updated criteria for AE-IPF. Also, bronchoalveolar lavage is no longer necessarily required for the diagnosis of AE in the 2016 criteria compared with the 2007 criteria. The new criteria provide a broader inclusion compared to the original 2007 criteria and make it easier to diagnose acute exacerbation (10). Figure 1 demonstrates computed tomography (CT) of the chest from a 68-year-old male patient who was admitted to the hospital for acute exacerbation of ILD.

Acute exacerbation in IPF is common and has a poor prognosis. The incidence of AE-IPF ranges from 4 to 20% per year among IPF patients in reported studies (3, 11). The wide variation in incidence of AE-IPF could be due to different definitions and criteria of acute exacerbation used by different authors. In one large retrospective study, 1- year and 3-year incidences of acute exacerbation in IPF were 14.2% and 20.7%, respectively (3).

The incidence, clinical characteristics and prognosis of acute exacerbation patients in CTD-ILD and other less common causes of ILD have yet to be fully studied as compared to acute exacerbation in IPF. The incidence of CTD-ILD exacerbation is less frequent than AE-IPF, however the prognosis of acute exacerbation in CTD-ILD is poor and comparable to the poor prognosis in IPF exacerbation. In one study six patients out of 83 CTD-ILD developed acute exacerbation of CTD-ILD with an overall incidence of 7.2% and a 1-year incidence 1.25%. Five out of the six patients died and one survived for discharge (12).

There is no standardized accepted approach to the treatment of AE-ILD, however, in clinical practice, some patients are treated with high dose immunosuppression, typically with pulse corticosteroids

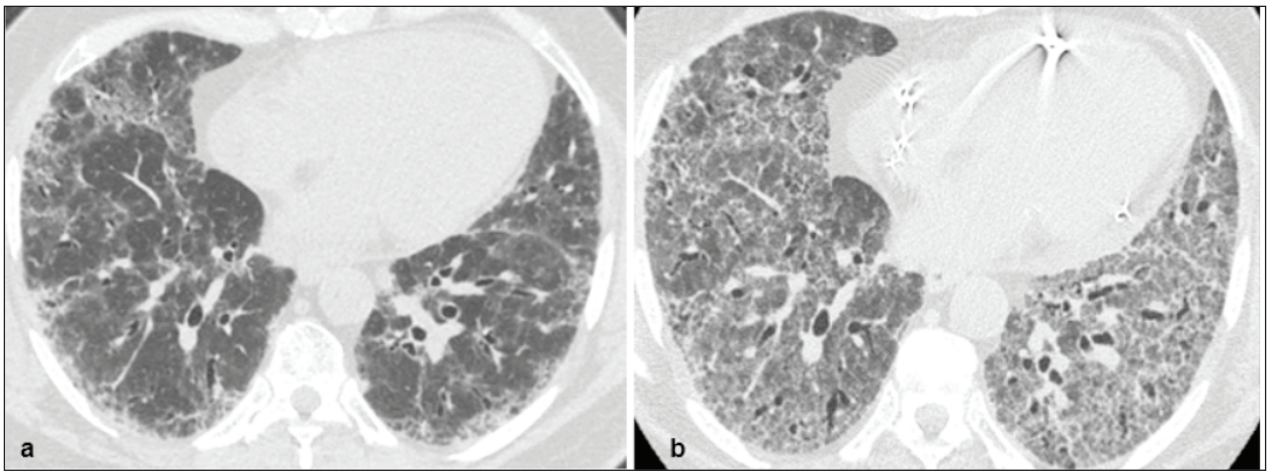

Figure 1. A: Axial CT of a patient with familial ILD. B: Axial CT of the same patient 6 months later at the time of an acute exacerbation and shows worsening bilateral ground-glass opacification. Abbreviation: CT, computed tomography, ILD: interstitial lung disease

of 500–1000 mg per day of methylprednisolone for three days along with antibiotics (13). The evidence for treating AE-ILD with corticosteroids is weak and some argue that it might be even harmful (14). It is reasonable to withhold treatment in patients with contraindications to therapy, as it is unclear how much this treatment affects outcomes (15). Other immunosuppressive agents, including cyclosporine A (CyA), tacrolimus, rituximab and intravenous CYC have also been used to treat AE-ILD. Newer therapies are being reported and investigated (6). Some patients also require mechanical ventilation support and mixed results have been reported from emergent lung transplantation (16).

Role of Cyclophosphamide in the Management of Chronic CTD-ILD

Cyclophosphamide is an alkylating agent and potent immunosuppressive medication that induces apoptotic cell death in rapidly proliferating cells, including clonally expanding lymphocytes (17). Cyclophosphamide can be administered orally or intravenously. In cases of rapidly progressive ILD, intravenous CYC has the advantage of a rapid onset of action, after which, maintenance therapy with an oral agent can be established (18, 19). Intravenous CYC has a favorable safety profile as compared to daily oral CYC. Daily oral CYC results in a higher cumulative dose, increasing the risk of side effects (17). The standard oral dosage for patients with normal renal function is 2 mg/kg/day and intravenous doses range between 500 and 1000 mg/m^2 body surface area administered every four to six weeks. Therapy generally is provided for six months to one year (20).

Cyclophosphamide is associated with significant toxicities and side effects. The most common side effects include nausea and hair thinning/alopecia. It is notorious for causing hemorrhagic cystitis and bladder cancer due to exposure of the bladder to acrolein, a metabolite of CYC. The risk of each is related to total cumulative dose, with a total dosage greater than 100 grams most strongly associated with bladder cancer. To reduce total dosage, duration of CYC usage is often limited to periods shorter than 12 months. Other side effects include bone marrow suppression with associated risks of bacterial and opportunistic infections, pulmonary toxicity, acute hepatic failure, cardiac toxicity, gonadal toxicity and an increase in hematological, solid and skin malignancies. CYC is teratogenic and should be avoided throughout pregnancy (20).

CYC has been widely studied in CTD-ILD, most commonly systemic sclerosis-interstitial lung disease (SSc-ILD) (21). In a treatment algorithm of SSc-ILD that was developed in 2016–2017, expert consensus was that intravenous CYC should be used as a second-line induction therapy, after mycophenolate mofetil (MMF) (22). To date, it has been studied in four randomized clinical trials in ILD (18, 23-25). The studies were mostly conducted in patients with SSc-ILD. It has also been suggested as a treatment option for severe, progressive disease or refractory

disease in rheumatoid arthritis-ILD (RA-ILD), idiopathic inflammatory myositis-ILD, and Sjögren's-associated ILD (26).

The first landmark randomized controlled trial that studied CYC in SSc-ILD was the Scleroderma Lung Study I (SLS I). It was a double-blind, randomized, placebo-controlled clinical trial that examined the efficacy of oral CYC for the treatment of SSc-ILD. One hundred fifty-eight subjects were randomized to oral CYC (up to 2 mg/kg/day) or placebo for 12 months. Of the 158 patients, 145 completed at least six months of treatment and were included in the analysis. The primary outcome was forced vital capacity (FVC). This study demonstrated a modest but statistically significant improvement in the mean absolute difference in FVC percent predicted between treatment and placebo group which was 2.53%, favoring CYC group (P<0.03). The mean absolute difference in total lung capacity (TLC) percent predicted was also significant (4.09%), favoring CYC group. There was no difference for DLCO and DLCO/VA. In addition, CYC had a modest beneficial effect on dyspnea, thickening of the skin, and the health-related quality of life. The SLS I study showed that the more extensive the lung fibrosis and/or skin involvement (FVC < 70% predicted, worse HRCT fibrosis score or worse skin thickening), the more likely the benefit from the medication (24). Sub-analysis of the SLS I trial revealed that CYC therapy was also associated with significant improvement in HRCT fibrosis score (27). Extension of the SLS I study published in 2007 showed that the favorable outcome of CYC on FVC continued to improve after cessation of CYC treatment reaching a maximum at 18 months (six months after stopping CYC therapy) with a mean 4.16% FVC difference versus placebo (p=0.01). The beneficial effects of CYC disappeared one year after CYC was terminated. In contrast, the positive effect on dyspnea persisted through 24 months (28). In the SLS I trial there was a higher frequency of adverse events (hematuria, leukopenia, neutropenia, anemia, and pneumonia) and higher withdrawal from treatment in the CYC arm compared with placebo, but there was no significant increase in serious adverse events (24). Based on this study, the European League Against Rheumatism (EULAR) has recommended that "cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with scleroderma with progressive ILD (strength of recommendation: A)" (29).

Due to the need for safer long-term treatment option, the SLS investigators conducted the Scleroderma Lung Study II (SLS II) which provided further insight into the role of MMF and CYC in patients with SSc-ILD. This study randomized patients in the United States to either two years of MMF or one year of oral CYC followed by one year of placebo. Patients in both arms had significant improvements in lung function over the two-year course of the study neither arm was superior over the other. Leukopenia and thrombocytopenia occurred less often in patients administered MMF than in those who received CYC. Similar to what was seen in the SLS I study, the more severe the fibrosis, the larger the effect of treatment (23).

In the third placebo-controlled trial using intravenous CYC, the Fibrosing Alveolitis in Scleroderma Trial (FAST), 45 patients were randomized to either receive placebo or intravenous CYC (600 mg/m2 body surface area intravenously at monthly intervals for six months) and oral prednisolone (20 mg on alternate days) followed by azathioprine (AZA) maintenance therapy (2.5 mg/kg/day). There was a numerical trend towards benefit in the treatment group with a 4.2% difference in FVC percent predicted, though it did not reach statistical significance (18). The difference in FVC was actually more pronounced in FAST than in SLS I (+4.2% vs. +2.5% respectively), but the smaller number of subjects in FAST (n=45) compared with SLS I (n=158) impacted the ability to achieve statistical significance. The increase in FVC in SLS I, SLS II, and FAST trial and other uncontrolled studies is supportive of efficacy of CYC in CTD-ILD (30).

The fourth randomized controlled trial by Zhang *et al*, compared intravenous CYC for 12 months versus MMF (1.5 g daily) for 12 months in 60 patients with SSc-ILD. All participants in intervention and control groups received prednisolone, with the starting dose titrated according to disease severity (as deemed by trial doctors) and all participants weaned to 10 mg daily within four weeks. A total of 45 patients completed this trial. Patients in both groups with FVC ≤ 75% predicted and forced expiratory volume in one second (FEV1) ≤ 75% predicted had significant statistical improvement in FVC and FEV1. Interestingly, for the patients with diffusion capacity for carbon monoxide (DLco) ≤ 65%, there were significant increases in the CYC group, which

has not been observed in the other trials (25).

In a recent Cochrane review that included the prior four studies, it was found that a small benefit may be achieved from the use of CYC in patients with CTD-ILD in mean difference in percent predicted FVC when compared with placebo, but not in the difference in the percent predicted DLco or mortality. Modest clinical improvement in dyspnea may be noted with the use of CYC (20). A randomized clinical trial of rituximab versus CYC in progressive CTD-ILD (including scleroderma-ILD, IIM-ILD, and MCTD-ILD), with change in FVC as the primary outcome, is currently going in the United Kingdom (RECITAL study, NCT01862926) (31).

Cyclophosphamide and ILD exacerbation

International guidelines for diagnosis and treatment of IPF state that supportive care remains the mainstay in the management of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF). However, some authors suggest the use of high-dose corticosteroid including methylprednisolone and prednisolone in treating of AE-IPF. This practice is mainly based on weak recommendations by international guidelines and not based in randomized controlled trials (32, 33). The use of immunosuppressants, including CYC and CyA have been reported in few retrospective studies and small case series. The addition of intravenous CYC to corticosteroid in AE-IPF has been listed as potential treatment option in the American Thoracic Society international working group report for AE-IPF and per the French practical guidelines (5, 8). The rationale for using CYC as immunosuppressant agent in AE-IPF was driven mainly by experience in other connective tissue diseases, such as SSc-ILD, and vasculitis (34, 35).

Okamoto *et al*, Ambusoni *et al*, and Parambil *et al* initially reported a total of 35 patients, with different definitions of AE-IPF, who used CYC and corticosteroids in addition to various supportive care measures for AE-IPF. These case series reported mixed results, and no clinically significant improved outcomes could be concluded from the data reported (36-38). Similarly, a 2004 retrospective study by Al-hameed *et al*, reviewed 25 patients who were admitted for AE-IPF with no identifiable cause. All patients died within the first 90 days of admission. All patients received treatment with corticosteroids. A smaller number (8 patients) were treated with immunosuppressive agents, predominantly CYC. Using corticosteroid and CYC did not seem to alter the prognosis in the previous cohort (39).

Two more recent small retrospective studies described the efficacy of corticosteroids and intravenous CYC therapy for AE-IPF. First study by Morawiec *et al*, who used high-dose pulses of corticosteroid followed by CYC regimen in 10 patients (with 11 episodes) with AE-IPF and seven IPF patients with sub-acute exacerbation (with an onset of symptoms between 30-90 days prior to treatment). The median age of the cohort was 67 years, and the median partial pressure of arterial oxygen to the fraction of inspired oxygen ratio ($PaO_2/FIO_{2)}$ at the time of exacerbation was 262. Treatment regimen was methylprednisolone pulses (1000 mg) at days 1 to 3 followed on day 4 by escalating regimen of CYC (initial intravenous dose 500 mg, increased by 200 mg every 2 weeks, maximum dose administered 1500 mg). All patients were alive one month after treatment was initiated. At three months, 72% of the patients were alive: all patients with sub-acute exacerbation and 55% patients with acute exacerbation. Cause of death was respiratory failure in all cases (40). The second study was also a small retrospective case series conducted in Italy. In this case series the authors evaluated the outcome in terms of survival of intravenous pulse doses of high-dose corticosteroid (methylprednisolone 1000 mg per day for three consecutive days) followed by monthly CYC administration (maximum six doses) in a cohort of patients with AE-IPF. A total of 11 patients were assessed. The median age of the cohort was 66 years, and the median PaO_2/FIO_2 at the time of exacerbation was 208. A median of 5 monthly pulse doses of CYC were administered, with 4 patients receiving all 6 doses. Four patients died before completion, and 3 patients developed adverse events (hematuria, epistaxis without thrombocytopenia and Pseudomonas pneumonia) and interrupted the pulse administration. Overall survival at three months was 73%, at six months was 63%, at 12 months was 55%, at 18 months was 45% and at two years was 27%. In-hospital mortality was 9% (35). Both studies suggested the potential benefit of corticosteroids plus intravenous CYC therapy considering the low side effects and the safety profile. However, their cohorts had small number of patients and they did not include a comparison group which makes it unclear if

corticosteroids plus intravenous CYC provide any benefit over other treatments.

A more recent study by Hozumi *et al*, published the largest retrospective, multicenter study about the use of CYC in AE-IPF. It included 102 patients with first episode of AE-IPF. The mean age of the cohort was 74 years and only 8 patients required intubation and mechanical ventilation. Based on propensity scores, 26 matched patient pairs were made. Efficacy of corticosteroids plus intravenous CYC therapy for the first acute exacerbation was compared with that of corticosteroid monotherapy. The post-acute exacerbation 90-day survival rate of their entire cohort was 65%. No significant differences between matched-group were observed in post-acute exacerbation 90-day survival rates (85% vs 77%; p = 0.70), cumulative survival rates, or incidence of adverse events. The authors concluded that the routine use of intravenous CYC with corticosteroids in AE-IPF was not beneficial when compared to corticosteroids alone (41). Another 2019 study by Aso *et al*, a Japanese inpatient database was utilized to study and analyze outcomes of patients with AE-IPF who received CYC in addition systemic corticosteroids, versus systemic corticosteroids alone. The results of an instrumental variable analysis showed no difference between the two groups in respect to in-hospital mortality and ventilator-free days (42). Table 1 summarizes these studies.

Due to the unmet need for effective treatment for AE-IPF and due to the lack of randomized controlled trials in this field, a phase III trial is being conducted. The EXAFIP study (NCT02460588) is a French national multicenter double-blind placebo-controlled randomized trial that is enrolling patients to evaluate the efficacy of CYC compared to placebo on early survival in patients treated with corticosteroids. The primary outcome is all-cause mortality rate at 3 months with other secondary outcomes. This

Table 1. Summary of the main studies that reported the use CYC in IPF exacerbation.

Study	Design	Size	Intervention	Clinical Outcome
Ambrosini et al. (2003)(37)	Single-center, retrospective study	5 patients	Steroids followed by CYC	Four patients died within one month, 1 patient lived at least 1.5 years.
Al-Hameed et al. (2004)(39)	Single-center, retrospective study	25 patients	Steroids or combination of steroids + CYC	All patients died in-hospital. One patient was discharged and returned after 30 days and died.
Parambil et al. (38)	Single-center, retrospective study	2 patients	Steroids followed by CYC	Both patients treated after biopsy. Both patients died in-hospital
Okamoto et al. (2006)(36)	Single-center, retrospective study	28 patients	Combination of steroids + CYC or Steroids + CyA	Twenty-four patients died within 4 months. Report did not specify whether the survivors received cyclophosphamide or cyclosporin. Survival rate at 1-month was 14% and 3-month was 14%.
Morawiec et al. (2011)(40)	Single-center, retrospective study	17 patients	Steroids followed by CYC	Ten patients had AE-IPF; survival rate at 1-month was 100%, at 3-month was 55%, and at 6-month was 40%. Seven patients had SAE-IPF, survival rate at 1-month was 100%, at 3-month was 100 %, and at 6-month was 71%.
Novelli et al. (2016)(35)	Single-center retrospective study	11 patients	Steroids + CYC	Survival rate at 3-month was 73%, at 6-month was 63%, at 12-month was 55%, at 18-month was 45% and at 2-year 27%.
Hozumi et al. (2019)(41)	Retrospective, multicenter study	102 patients	Steroid versus steroids plus CYC	No significant differences in 90-day survival rate between matched groups.
Aso et al. (2019)(42)	Retrospective, nationwide data base study	1847 patients	Steroids versus steroids + CYC	No significant differences between the two groups with respect to in-hospital mortality.

AE-IPF: acute exacerbation of idiopathic pulmonary fibrosis, SAE-IPF: subacute exacerbation of idiopathic pulmonary fibrosis, CI: calcineurin inhibitor, CyA: cyclosporin A, CYC: cyclophosphamide, TAC: tacrolimus.

study should provide better insights on the efficacy and side effects of CYC in AE-IPF (43).

With regards the treatment approach for acute exacerbation in CTD-ILD, it has not yet been established but conventionally it is treated with corticosteroids (12). Other drugs have been additionally administered including CyA with inconsistent outcomes (44, 45). In a retrospective study by Suda *et al*, six patients with CTD-ILD were treated with high dose corticosteroids. Four of 6 patients were given IV 500–750 mg/m2 CYC and 2 received 2–3 mg/kg/day CyA. In the previous cohort, all patients required mechanical ventilation and 5 of 6 died. The patient who survived only received corticosteroids (12). Tomiyama *et al*, reported 13 case of SSc-ILD exacerbation. Ten patients were treated with CYC in combination with corticosteroids or other immunosuppressant. Mortality was high in the previous cohort as it was 46% (46).

Ota *et al*, retrospectively reviewed 17 patients with RA-ILD who required hospitalization at the University of Tokyo Hospital due to an acute exacerbation (12 patients) or subacute exacerbation (5 patients). Patients were classified into four groups: patients who received glucocorticoids only, glucocorticoids plus tacrolimus, glucocorticoids plus CyA, or CYC in combination with other drugs. Five patients received intravenous CYC with dose varying between 750 to 1200 mg. The total number of doses also varied between 2 to 9 doses. Interestingly, the patients who received CyA or CYC had more severe disease compared to other treatment group, and all five patients in the CYC group were alive for the average observation period of 474 days. It is difficult to discriminate whether the better prognosis in this group was due to CYC alone or combination of some drugs. The authors concluded that for severe cases with low respiratory function, intensive therapy, including CYC, has a potential to improve the prognosis the acute exacerbation of RA-ILD (47).

Schulze *et al*, identified 14 patients who were admitted to the intensive care unit with severe ILD and were treated with cyclophosphamide. Twelve patients were mechanically ventilated, and 7 patients were supported by extracorporeal membrane oxygenation. Corticosteroids and antibiotics were given to all patients. The absolute cyclophosphamide doses varied from 400 mg up to 1.000 mg (mean dose 807.1 mg) and the mean time between diagnosis and the initiation of cyclophosphamide was 11.3 days. Five patients received plasmapheresis. The authors observed a positive prognostic effect in patients with SSc and ANCA-associated-vasculitis and reduced overall survival was found for Goodpasture syndrome, dermatomyositis, cryptogenic organizing pneumonia and drug reaction with eosinophilia and systemic symptoms. They also concluded that additional plasmapheresis and initiation of cyclophosphamide within ten days following initial diagnosis of ILD were associated with improved prognosis (48). Table 2 summarizes the previous studies.

Conclusion and Consideration for Future Research

Cyclophosphamide has been shown to have a beneficial effect in the chronic management of scleroderma-ILD in landmark randomized controlled

Table 2: Summary of the main studies examing the use of CYC in CTD-ILD exacerbation

Study	Design	Size	Intervention	Clinical outcome
Suda et al. (2009)(12)	Retrospective, single center	6 patients	Steroids or combination of steroids + CYC or steroids + CyA	Five patients died. The patient who survived received only steroids.
Tomiyama et al. (2016)(46)	Single-center, Retrospective study	13 patients	Steroids or combination of steroids + CYC or steroids + CI	Twelve patients received combination therapy. Almost half of the patients died on follow up.
Ota el al. (2017)(47)	Single-center, Retrospective study	17 patients	Steroid or combination of steroids + TAC or steroids + CyA or steroids + CYC (or combination of more than 2 immunosuppressants)	The five patients who received CYC had more severe disease and were alive at 474 days follow up.
Schulze et al. (2019) (48)	Single-center, Retrospective study	14 patients	Steroid + CYC or steroid + CYC + plasmapheresis	Patients with Scc-ILD and ANCA-associated-vasculitis ILD had an improved survival.

CI: calcineurin inhibitor, CyA: cyclosporin A, CYC: cyclophosphamide, TAC: tacrolimus

trials (18, 23-25). Although this effect was beneficial for the groups studied, it was modest in terms of lung function improvement and was mainly confined to progressive cases of SSc-ILD. However, for AE-ILD, we found retrospective and small studies with a few cases and non-comparative groups. They showed mixed results and did not show definite benefit in AE-IPF or CTD-ILD (12, 35-42, 46-48).

Decision-making in the treatment of people with lung fibrosis in the setting of acute exacerbation is unclear, and there are still questions that need to be answered in this field. The clinician must balance a high level of need for therapy in a severely sick population against the potential for adverse effects as CYC is well known for wide range of toxicities. It is not clear whether evidence of efficacy of CYC in progressive CTD-ILD can be extrapolated to the acute exacerbation at this time.

Conflict of Interest: The authors declare no conflict of interest.

Funding: None

Author Contributions: All authors contributed to the study conception and design. The first draft of the manuscript was written by Ayoub Innabi, MD, Divya C. Patel, DO. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. P. Spagnolo, W. Wuyts, Acute exacerbations of interstitial lung disease: lessons from idiopathic pulmonary fibrosis, Curr Opin Pulm Med 23(5) (2017) 411-417.
2. I.N. Park, D.S. Kim, T.S. Shim, C.M. Lim, S.D. Lee, Y. Koh, W.S. Kim, W.D. Kim, S.J. Jang, T.V. Colby, Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis, Chest 132(1) (2007) 214-20.
3. J.W. Song, S.B. Hong, C.M. Lim, Y. Koh, D.S. Kim, Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome, Eur Respir J 37(2) (2011) 356-63.
4. Y. Toyoda, M. Hanibuchi, J. Kishi, H. Kawano, S. Morizumi, S. Sato, M. Kondo, T. Takikura, T. Tezuka, H. Goto, Y. Nishioka, Clinical features and outcome of acute exacerbation of interstitial pneumonia associated with connective tissue disease, J Med Invest 63(3-4) (2016) 294-9.
5. V. Cottin, B. Crestani, D. Valeyre, B. Wallaert, J. Cadranel, J.C. Dalphin, P. Delaval, D. Israel-Biet, R. Kessler, M. Reynaud-Gaubert, B. Aguilaniu, B. Bouquillon, P. Carré, C. Danel, J.B. Faivre, G. Ferretti, N. Just, S. Kouzan, F. Lebargy, S. Marchand-Adam, B. Philippe, G. Prévot, B. Stach, F. Thivolet-Béjui, J.F. Cordier, F.N.R. Centre, N.o.C.C.f.R.L. Diseases, Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines, Eur Respir Rev 23(132) (2014) 193-214.
6. W.H. Amundson, E. Racila, T. Allen, H.E. Dincer, R. Tomic, M. Bhargava, D.M. Perlman, H.J. Kim, Acute exacerbation of interstitial lung disease after procedures, Respir Med 150 (2019) 30-37.
7. W.D. Travis, U. Costabel, D.M. Hansell, T.E. King, D.A. Lynch, A.G. Nicholson, C.J. Ryerson, J.H. Ryu, M. Selman, A.U. Wells, J. Behr, D. Bouros, K.K. Brown, T.V. Colby, H.R. Collard, C.R. Cordeiro, V. Cottin, B. Crestani, M. Drent, R.F. Dudden, J. Egan, K. Flaherty, C. Hogaboam, Y. Inoue, T. Johkoh, D.S. Kim, M. Kitaichi, J. Loyd, F.J. Martinez, J. Myers, S. Protzko, G. Raghu, L. Richeldi, N. Sverzellati, J. Swigris, D. Valeyre, A.E.C.o.I.I. Pneumonias, An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, Am J Respir Crit Care Med 188(6) (2013) 733-48.
8. H.R. Collard, C.J. Ryerson, T.J. Corte, G. Jenkins, Y. Kondoh, D.J. Lederer, J.S. Lee, T.M. Maher, A.U. Wells, K.M. Antoniou, J. Behr, K.K. Brown, V. Cottin, K.R. Flaherty, J. Fukuoka, D.M. Hansell, T. Johkoh, N. Kaminski, D.S. Kim, M. Kolb, D.A. Lynch, J.L. Myers, G. Raghu, L. Richeldi, H. Taniguchi, F.J. Martinez, Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report, Am J Respir Crit Care Med 194(3) (2016) 265-75.
9. H.R. Collard, B.B. Moore, K.R. Flaherty, K.K. Brown, R.J. Kaner, T.E. King, J.A. Lasky, J.E. Loyd, I. Noth, M.A. Olman, G. Raghu, J. Roman, J.H. Ryu, D.A. Zisman, G.W. Hunninghake, T.V. Colby, J.J. Egan, D.M. Hansell, T. Johkoh, N. Kaminski, D.S. Kim, Y. Kondoh, D.A. Lynch, J. Müller-Quernheim, J.L. Myers, A.G. Nicholson, M. Selman, G.B. Toews, A.U. Wells, F.J. Martinez, I.P.F.C.R.N. Investigators, Acute exacerbations of idiopathic pulmonary fibrosis, Am J Respir Crit Care Med 176(7) (2007) 636-43.
10. N. Enomoto, Y. Oyama, Y. Enomoto, H. Yasui, M. Karayama, M. Kono, H. Hozumi, Y. Suzuki, K. Furuhashi, T. Fujisawa, N. Inui, Y. Nakamura, T. Suda, Differences in clinical features of acute exacerbation between connective tissue disease-associated interstitial pneumonia and idiopathic pulmonary fibrosis, Chron Respir Dis 16 (2019) 1479972318809476.
11. C.J. Ryerson, V. Cottin, K.K. Brown, H.R. Collard, Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm, Eur Respir J 46(2) (2015) 512-20.
12. T. Suda, Y. Kaida, Y. Nakamura, N. Enomoto, T. Fujisawa, S. Imokawa, H. Hashizume, T. Naito, D. Hashimoto, Y. Takehara, N. Inui, H. Nakamura, T.V. Colby, K. Chida, Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases, Respir Med 103(6) (2009) 846-53.
13. G. Leuschner, J. Behr, Acute Exacerbation in Interstitial Lung Disease, Front Med (Lausanne) 4 (2017) 176.
14. S.A. Papiris, E.D. Manali, L. Kolilekas, C. Triantafillidou, I. Tsangaris, K. Kagouridis, Steroids in idiopathic pulmonary fibrosis acute exacerbation: defenders or killers?, Am J Respir Crit Care Med 185(5) (2012) 587-8.
15. S. Cuerpo, J. Moisés, F. Hernández-González, M. Benegas, J. Ramirez, M. Sánchez, À. Agustí, J. Sellares, Acute exacerbations of idiopathic pulmonary fibrosis: Does clinical stratification or steroid treatment matter?, Chron Respir Dis 16 (2019) 1479973119869334.
16. J.S. Lee, A. Fischer, Current and emerging treatment options for interstitial lung disease in patients with rheumatic disease, Expert Rev Clin Immunol 12(5) (2016) 509-20.
17. A.S. Jee, T.J. Corte, Current and Emerging Drug Therapies for Connective Tissue Disease-Interstitial Lung Disease (CTD-ILD), Drugs 79(14) (2019) 1511-1528.
18. R.K. Hoyles, R.W. Ellis, J. Wellsbury, B. Lees, P. Newlands, N.S. Goh, C. Roberts, S. Desai, A.L. Herrick, N.J. McHugh, N.M. Foley, S.B. Pearson, P. Emery, D.J. Veale, C.P. Denton, A.U. Wells, C.M. Black, R.M. du Bois, A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma, Arthritis Rheum 54(12) (2006) 3962-70.
19. T.J. Corte, R. Ellis, E.A. Renzoni, D.M. Hansell, A.G. Nicholson, R.M. du Bois, A.U. Wells, Use of intravenous cyclophosphamide in known or suspected, advanced non-specific interstitial pneumonia,

Sarcoidosis Vasc Diffuse Lung Dis 26(2) (2009) 132-8.
20. H. Barnes, A.E. Holland, G.P. Westall, N.S. Goh, I.N. Glaspole, Cyclophosphamide for connective tissue disease-associated interstitial lung disease, Cochrane Database Syst Rev 1 (2018) CD010908.
21. A. Perelas, A.V. Arrossi, K.B. Highland, Pulmonary Manifestations of Systemic Sclerosis and Mixed Connective Tissue Disease, Clin Chest Med 40(3) (2019) 501-518.
22. A. Fernández-Codina, K.M. Walker, J.E. Pope, S.A. Group, Treatment Algorithms for Systemic Sclerosis According to Experts, Arthritis Rheumatol 70(11) (2018) 1820-1828.
23. D.P. Tashkin, M.D. Roth, P.J. Clements, D.E. Furst, D. Khanna, E.C. Kleerup, J. Goldin, E. Arriola, E.R. Volkmann, S. Kafaja, R. Silver, V. Steen, C. Strange, R. Wise, F. Wigley, M. Mayes, D.J. Riley, S. Hussain, S. Assassi, V.M. Hsu, B. Patel, K. Phillips, F. Martinez, J. Golden, M.K. Connolly, J. Varga, J. Dematte, M.E. Hinchcliff, A. Fischer, J. Swigris, R. Meehan, A. Theodore, R. Simms, S. Volkov, D.E. Schraufnagel, M.B. Scholand, T. Frech, J.A. Molitor, K. Highland, C.A. Read, M.J. Fritzler, G.H.J. Kim, C.H. Tseng, R.M. Elashoff, S.L.S.I. Investigators, Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial, Lancet Respir Med 4(9) (2016) 708-719.
24. D.P. Tashkin, R. Elashoff, P.J. Clements, J. Goldin, M.D. Roth, D.E. Furst, E. Arriola, R. Silver, C. Strange, M. Bolster, J.R. Seibold, D.J. Riley, V.M. Hsu, J. Varga, D.E. Schraufnagel, A. Theodore, R. Simms, R. Wise, F. Wigley, B. White, V. Steen, C. Read, M. Mayes, E. Parsley, K. Mubarak, M.K. Connolly, J. Golden, M. Olman, B. Fessler, N. Rothfield, M. Metersky, S.L.S.R. Group, Cyclophosphamide versus placebo in scleroderma lung disease, N Engl J Med 354(25) (2006) 2655-66.
25. G. Zhang, T. Xu, H. Zhang, S. Ye, Q. Wang, L. Zhang, Y. Lei, R. Luo, X. Zhang, [Randomized control multi-center clinical study of mycophenolate mofetil and cyclophosphamide in the treatment of connective tissue disease related interstitial lung disease], Zhonghua Yi Xue Za Zhi 95(45) (2015) 3641-5.
26. B. Wallace, D. Vummidi, D. Khanna, Management of connective tissue diseases associated interstitial lung disease: a review of the published literature, Curr Opin Rheumatol 28(3) (2016) 236-45.
27. J. Goldin, R. Elashoff, H.J. Kim, X. Yan, D. Lynch, D. Strollo, M.D. Roth, P. Clements, D.E. Furst, D. Khanna, S. Vasunilashorn, G. Li, D.P. Tashkin, Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study, Chest 136(5) (2009) 1333-1340.
28. D.P. Tashkin, R. Elashoff, P.J. Clements, M.D. Roth, D.E. Furst, R.M. Silver, J. Goldin, E. Arriola, C. Strange, M.B. Bolster, J.R. Seibold, D.J. Riley, V.M. Hsu, J. Varga, D. Schraufnagel, A. Theodore, R. Simms, R. Wise, F. Wigley, B. White, V. Steen, C. Read, M. Mayes, E. Parsley, K. Mubarak, M.K. Connolly, J. Golden, M. Olman, B. Fessler, N. Rothfield, M. Metersky, D. Khanna, N. Li, G. Li, S.L.S.R. Group, Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease, Am J Respir Crit Care Med 176(10) (2007) 1026-34.
29. O. Kowal-Bielecka, J. Fransen, J. Avouac, M. Becker, A. Kulak, Y. Allanore, O. Distler, P. Clements, M. Cutolo, L. Czirjak, N. Damjanov, F. Del Galdo, C.P. Denton, J.H.W. Distler, I. Foeldvari, K. Figelstone, M. Frerix, D.E. Furst, S. Guiducci, N. Hunzelmann, D. Khanna, M. Matucci-Cerinic, A.L. Herrick, F. van den Hoogen, J.M. van Laar, G. Riemekasten, R. Silver, V. Smith, A. Sulli, I. Tarner, A. Tyndall, J. Welling, F. Wigley, G. Valentini, U.A. Walker, F. Zulian, U. Müller-Ladner, E. Coauthors, Update of EULAR recommendations for the treatment of systemic sclerosis, Ann Rheum Dis 76(8) (2017) 1327-1339.
30. S.C. Mathai, S.K. Danoff, Management of interstitial lung disease associated with connective tissue disease, BMJ 352 (2016) h6819.
31. P. Saunders, V. Tsipouri, G.J. Keir, D. Ashby, M.D. Flather, H. Parfrey, D. Babalis, E.A. Renzoni, C.P. Denton, A.U. Wells, T.M. Maher, Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial, Trials 18(1) (2017) 275.
32. G. Raghu, H.R. Collard, J.J. Egan, F.J. Martinez, J. Behr, K.K. Brown, T.V. Colby, J.F. Cordier, K.R. Flaherty, J.A. Lasky, D.A. Lynch, J.H. Ryu, J.J. Swigris, A.U. Wells, J. Ancochea, D. Bouros, C. Carvalho, U. Costabel, M. Ebina, D.M. Hansell, T. Johkoh, D.S. Kim, T.E. King, Y. Kondoh, J. Myers, N.L. Müller, A.G. Nicholson, L. Richeldi, M. Selman, R.F. Dudden, B.S. Griss, S.L. Protzko, H.J. Schünemann, A.E.J.A.C.o.I.P. Fibrosis, An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, Am J Respir Crit Care Med 183(6) (2011) 788-824.
33. M.M. Juarez, A.L. Chan, A.G. Norris, B.M. Morrissey, T.E. Albertson, Acute exacerbation of idiopathic pulmonary fibrosis-a review of current and novel pharmacotherapies, J Thorac Dis 7(3) (2015) 499-519.
34. K. de Groot, L. Harper, D.R. Jayne, L.F. Flores Suarez, G. Gregorini, W.L. Gross, R. Luqmani, C.D. Pusey, N. Rasmussen, R.A. Sinico, V. Tesar, P. Vanhille, K. Westman, C.O. Savage, E.E.V.S. Group), Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial, Ann Intern Med 150(10) (2009) 670-80.
35. L. Novelli, R. Ruggiero, F. De Giacomi, A. Biffi, P. Faverio, L. Bilucaglia, S. Gamberini, G. Messinesi, A. Pesci, Corticosteroid and cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: a single center experience and literature review, Sarcoidosis Vasc Diffuse Lung Dis 33(4) (2016) 385-391.
36. T. Okamoto, H. Ichiyasu, K. Ichikado, H. Muranaka, K. Sato, S. Okamoto, K. Iyonaga, M. Suga, H. Kohrogi, [Clinical analysis of the acute exacerbation in patients with idiopathic pulmonary fibrosis], Nihon Kokyuki Gakkai Zasshi 44(5) (2006) 359-67.
37. V. Ambrosini, A. Cancellieri, M. Chilosi, M. Zompatori, R. Trisolini, L. Saragoni, V. Poletti, Acute exacerbation of idiopathic pulmonary fibrosis: report of a series, Eur Respir J 22(5) (2003) 821-6.
38. J.G. Parambil, J.L. Myers, J.H. Ryu, Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy, Chest 128(5) (2005) 3310-5.
39. F.M. Al-Hameed, S. Sharma, Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis, Can Respir J 11(2) (2004) 117-22.
40. E. Morawiec, I. Tillie-Leblond, V. Pansini, J. Salleron, M. Remy-Jardin, B. Wallaert, Exacerbations of idiopathic pulmonary fibrosis treated with corticosteroids and cyclophosphamide pulses, Eur Respir J 38(6) (2011) 1487-9.
41. H. Hozumi, H. Hasegawa, K. Miyashita, H. Yasui, Y. Suzuki, M. Kono, M. Karayama, K. Furuhashi, D. Hashimoto, N. Enomoto, T. Fujisawa, N. Inui, Y. Nakamura, K. Yokomura, H. Nakamura, T. Suda, Efficacy of corticosteroid and intravenous cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: A propensity score-matched analysis, Respirology 24(8) (2019) 792-798.
42. S. Aso, H. Matsui, K. Fushimi, H. Yasunaga, Systemic glucocorticoids plus cyclophosphamide for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective nationwide study, Sarcoidosis Vasc Diffuse Lung Dis 36(2) (2019) 116-123.
43. J.M. Naccache, M. Montil, J. Cadranel, M. Cachanado, V. Cottin, B. Crestani, D. Valeyre, B. Wallaert, T. Simon, H. Nunes, Study protocol: exploring the efficacy of cyclophosphamide added to corticosteroids for treating acute exacerbation of idiopathic pulmonary fibrosis; a randomized double-blind, placebo-controlled, multi-center phase III trial (EXAFIP), BMC Pulm Med 19(1) (2019) 75.
44. B. Bradley, H.M. Branley, J.J. Egan, M.S. Greaves, D.M. Hansell, N.K. Harrison, N. Hirani, R. Hubbard, F. Lake, A.B. Millar, W.A. Wallace, A.U. Wells, M.K. Whyte, M.L. Wilsher, B.i.T.S.S.o.C.C.

British Thoracic Society Interstitial Lung Disease Guideline Group, T.S.o. Australia, N.Z.T. Society, I.T. Society, 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 63 Suppl 5 (2008) v1-58.
45. S.M. Koo, S.Y. Kim, S.M. Choi, H.K. Lee, K.I.L.D.S. Group, Korean Guidelines for Diagnosis and Management of Interstitial Lung Diseases: Part 5. Connective Tissue Disease Associated Interstitial Lung Disease, Tuberc Respir Dis (Seoul) 82(4) (2019) 285-297.
46. F. Tomiyama, R. Watanabe, T. Ishii, Y. Kamogawa, Y. Fujita, Y. Shirota, K. Sugimura, H. Fujii, H. Harigae, High Prevalence of Acute Exacerbation of Interstitial Lung Disease in Japanese Patients with Systemic Sclerosis, Tohoku J Exp Med 239(4) (2016) 297-305.
47. M. Ota, Y. Iwasaki, H. Harada, O. Sasaki, Y. Nagafuchi, S. Nakachi, S. Sumitomo, H. Shoda, S. Tohma, K. Fujio, K. Yamamoto, Efficacy of intensive immunosuppression in exacerbated rheumatoid arthritis-associated interstitial lung disease, Mod Rheumatol 27(1) (2017) 22-28.
48. A.B. Schulze, G. Evers, A. Kümmel, F. Rosenow, J. Sackarnd, J.P. Hering, C. Schülke, J.A. Engelbertz, D. Görlich, P.J. Barth, G. Lenz, H. Becker, M. Mohr, L.H. Schmidt, Cyclophosphamide pulse therapy as treatment for severe interstitial lung diseases, Sarcoidosis Vasc Diffuse Lung Dis 36(2) (2019) 157-166.