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REVIEW

Efficacy of cyclophosphamide in treating connective tissue disease-related interstitial lung diseases

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Abstract

Interstitial lung diseases (ILDs) are some of the first and most serious complications of connective tissue diseases (CTDs). However, the pathogenesis of CTD-related ILDs (CTD-ILDs) is still unclear and their treatment often depends on functional and radiographic disease progression as well as on patient age and comorbidities. It can be difficult to manage CTD-ILDs due to their heterogeneous nature, the lack of robust therapeutic data, and the few well-defined outcome measures. This review focuses on cyclophosphamide due to its crucial role in the treatment of systemic sclerosis-related ILD, particularly in the case of patients with progressive ILD. This narrative review was performed using PubMed, Medline, and Cochrane Library databases to retrieve English language papers published between 2000 and April 2020 concerning the treatment of CTD-ILDs with cyclophosphamide.

Keywords: comorbidities, connective tissue diseases, cyclophosphamide, disease-modifying antirheumatic drugs, interstitial lung diseases.

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Introduction

Interstitial lung diseases (ILDs) are among the principal complications of connective tissue diseases (CTDs) and one of the main causes of mortality.[1] ILDs may be associated with any CTD but are most frequent in patients with systemic sclerosis (SSc), whose evolution and treatment have been the most widely studied, and are often encountered in those with Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), or polymyositis (PM)/dermatomyositis (DM). Different CTDs are associated with different ILDs with variations in disease progression and outcomes:[1] SSc patients are mainly affected by non-specific interstitial pneumonia (NSIP); patients with PM show patterns ranging from organizing pneumonia to NSIP or usual interstitial pneumonia (UIP) and those with mixed CTD (MCTD) or primary SS least frequently develop ILD (Table 1). It is interesting to note that UIP is also the most frequent histological model of rheumatoid arthritis (RA)-related ILD, but it is much less frequent in patients with SSc-related or other CTD-related ILDs. The radiographic pattern of UIP is characterized by bilateral subpleural reticulation, with or without honeycombing; NSIP is mainly characterized by ground-glass opacities and often associated with signs of fibrosis (reduced lobar volume, reticulation, and/or traction bronchiectasis). The distinction between UIP and NSIP is important because of the poor prognosis of idiopathic UIP and the lack of an effective medical treatment compared to the better prognosis of idiopathic NSIP and its common response to glucocorticoids (GCs).[1]

This narrative review focuses on cyclophosphamide (CYC) due to its crucial role in the treatment of SSc-related ILD, particularly in the case of patients with progressive ILD. Therefore, it summarizes the published data concerning the efficacy of CYC in treating CTD-related lung involvement.

Methodology

The terms 'lung' or 'pulmonary', 'pulmonary hypertension', 'connective tissue disease', 'scleroderma', 'systemic lupus erythematosus', 'Sjögren's syndrome', 'mixed connective tissue disease', 'rheumatologic(al) disease', 'interstitial lung disease', 'idiopathic inflammatory myositis', 'polymyositis', 'dermatomyositis', 'myositis', 'treatment', 'therapy', 'cyclophosphamide', and 'management' were used to search the Medline, PubMed, and Cochrane Library databases for English language papers published between 2000 and

Table 1. Features of interstitial lung disease in connective tissue diseases.

Connective tissue disease	Characteristics
Systemic sclerosis	NSIP >> UIP Association with nucleolar pattern of ANA, anti-SCL70, anti-Th/To, anti-U3RNP, and anti-PM-SCL antibodies Consider PFT and HRCT in all patients at time of diagnosis
Idiopathic interstitial myopathy	NSIP >> UIP Dermatomyositis > polymyositis More frequently with anti-synthetase antibodies
Mixed connective tissue disease	NSIP >> UIP Usually associated with systemic sclerosis-type clinical findings and antibodies
Sjögren's syndrome	NSIP most frequent, but LIP, OP, or UIP also seen Pulmonary lymphoma must also be considered
Systemic lupus erythematosus	NSIP >> LIP and OP >>> UIP (very uncommon) Must be distinguished from alveolar haemorrhage (rare) and lupus pneumonitis (1–10%)

ANA, antinuclear antibodies; HRCT, high-resolution CT; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; PFTs, pulmonary function tests; UIP, usual interstitial pneumonia.

March 2020. The papers' references were also reviewed as were textbook chapters.

Pathogenesis

Although the aetiology of CTD-ILD is unknown, various hypotheses have been proposed mainly by extrapolating the findings of studies of SSc patients. One of these is that environmental pathogens trigger inflammation, drive inflammatory cells into alveolar and interstitial spaces, and cause possibly significant damage to the alveolar epithelium.[2,3] This may explain why patients with SSc show higher serum levels of surfactant protein D and Krebs von den Lungen-6, two glycoproteins expressed by type II alveolar cells and used as biomarkers of pulmonary epithelium damage.[4] It is likely that the entity of the effect particularly on the layers of the lung extracellular matrix that govern alveolar structure determines the extent of the recovery of lung structure and function.[5]

As a result of inflammation and epithelial damage, lung fibroblasts and myofibroblasts are recruited and activated to increase the production of extracellular matrix proteins and populate fibrogenic lung cell scarring,[6] a role that is confirmed by the absence of lung fibrosis in experimental models of mice that have been genetically modified in order to attenuate their responsiveness to or signalling of transforming growth factor-β.[7] There may also be lung epithelial cells among the pro-fibrotic mesenchymal cells characterizing lung fibrosis as the existence of epithelial/mesenchymal trans-differentiation has been clearly shown in many studies and, although its precise role is still unknown,[8] its pattern and type of fibrotic reaction depend on its duration.

It has also been hypothesized that some CTDs begin as a result of lung damage triggering local inflammation and inducing auto-antigen expression, thus leading to the generation of pulmonary auto-antibodies. Further lung inflammation and fibrosis is then caused by the binding of disease-associated auto-antibodies, a process that can be perpetuated by antigens.[9]

Systemic sclerosis

SSc is a rare CTD characterized by vasculopathy and progressive fibrosis of the skin and internal organs. It is categorized as limited cutaneous SSc (lcSSc) when the skin fibrosis only affects the face, feet, hands, and forearms and as diffuse cutaneous SSc (dcSSc) when it extends to the trunk and to areas proximal to the elbows. One of the main features of SSc is ILD, which usually appears early and is now a classification criterion.[10] The risk factors for its development and progression are dcSSc, Afro-American ethnicity, developing SSc more recently and being diagnosed at an older age, the presence of anti-Scl-70/anti-topoisomerase I antibodies, and the absence of anti-centromere antibodies.[11]

Given the prevalence of lung complications, all SSc patients should undergo high-resolution CT (HRCT) and pulmonary function tests (PFTs) to identify lung involvement as early as possible. The most frequent HRCT pattern is NSIP, whereas the PFTs of patients with SSc and ILD usually reveal reduced forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO).[12] SSc-ILD is associated with greater mortality: an American study has found that ILD is the most frequent cause of death[13] and an analysis of 5850 patients in the European League Against Rheumatism (EULAR) Scleroderma Trials and Research database has shown that 35% of SSc-related deaths

between 2004 and 2008 were attributable to lung fibrosis.[14] The clinical course of SSc-ILD varies from slowly but progressively decreasing lung function to rapidly worsening disease.[15]

Treatment

The results of observational studies indicate that death is five times more likely among patients with ILD and pulmonary arterial hypertension (PAH) than among those with SSc and PAH.[16,17] Various drugs have been used to treat CTD-ILD, but data from small-scale pilot studies and randomized controlled trials (RCTs) show that the alkylating agent CYC is effective because it has a highly potent immunosuppressive effect by interfering with the cell cycle.

Oral cyclophosphamide

The double-blind, randomized, placebo-controlled Scleroderma Lung Study (SLS), conducted in 13 centres in the United States, was one of the first trials to assess the safety and efficacy of CYC in treating SSc-ILD.[18] SLS involved 158 patients with lcSSc or dcSSc and active alveolitis revealed by means of bronchoalveolar lavage or ground-glass opacities detected by means of HRCT. The patients were administered oral CYC 1 mg/kg of body weight/day (increasing monthly to 2 mg/kg) or placebo for 1 year and then followed up for 12 months, during which time they did not receive any study medication.

The 12-month treatment schedule was completed by 54 patients in the CYC group and 55 in the placebo group:[18] the adjusted mean absolute between-group difference in FVC at the end of the treatment period was 2.53% (95% confidence interval (CI) 0.28–4.79; $p<0.03$) in favour of CYC, which increased to 2.97% (95% CI 0.75–5.19; $p=0.009$) when baseline FVC and the worst baseline HRCT fibrosis score were included in the model. A regression analysis of the 12-month effect of lung fibrosis on FVC showed a greater decline in patients treated with placebo with more severe fibrosis (–2.01% of predicted per unit fibrosis score ($p=0.006$)), whereas the slope was not significant in the CYC group ($p=0.26$), thus suggesting that more severe baseline fibrosis is more likely to evolve into progressive ILD in the absence of treatment. Importantly, the between-group difference in the slopes was significant ($p=0.009$), indicating that CYC had a protective effect on the reduction of FVC. There was also a significant 4.09% between-group difference in predicted total lung capacity in favour of CYC ($p=0.026$), but no significant effect on gas transfer (DLCO or the ratio of diffusing capacity to alveolar volume (DLCO to VA ratio)). The dyspnoea index improved by >1 unit in the CYC group and worsened by >1 unit in the placebo group.[18] Despite the greater number of adverse events in the patients treated with CYC, the authors concluded that the risk-to-benefit ratio was favourable.[18]

Forty-eight of the 54 patients in the CYC group and 45 of the 55 patients in the placebo group who completed the 12-month treatment period as well as 9 and 11 non-completers, respectively, were monitored for a further year in the absence of the study treatment. At the end of this monitoring period, data analysis by Tashkin et al.[19] showed that the mean predicted FVC% and total lung capacity% were nearly the same in the two patient groups, as was the predicted DLCO% and DLCO to VA ratio. Interestingly, the between-group difference in the predicted FVC% of patients with more severe disease at baseline was no longer significant and, although there was no longer any beneficial effect of CYC on lung diffusion, the patients reported a beneficial impact on dyspnoea as measured by dyspnoea scores.[19] Skin thickness scores, which had considerably improved in the dcSSc patients treated with CYC for 12 months, decreased to approximately the same extent in both groups between months 12 and 18 but seemed to have slightly increased in the CYC group by month 24. Furthermore, the between-group difference in the Health Assessment Questionnaire-Disability Index, which had been significant after 12 months, was no longer significant ($p<0.275$). The main adverse events were haematuria (one CYC-treated patient and two placebo-treated patients, one of whom received CYC in the second year), anaemia (two CYC-treated patients, one of whom continued taking CYC in the second year, and one placebo-treated patient), and pneumonia (one CYC-treated patient).[19]

In conclusion, although the SLS demonstrated a beneficial effect of 1-year administration of oral CYC on lung function, the short duration of this effect suggested that the treatment should be considered cautiously on the basis of its potential risk-to-benefit ratio.

Intravenous cyclophosphamide

Due to the side effects of oral CYC, Hoyles et al.[20] assessed the efficacy of intravenous (i.v.) CYC in treating SSc-ILD in the Fibrosing Alveolitis in Scleroderma Trial, which was conducted in five UK centres between 1999 and 2003, and analysed the effects of treatment with GCs and i.v. CYC followed by oral azathioprine (AZA). Twenty-two of the 45 selected patients (15 with lcSSc) were randomized to receive oral prednisolone 20 mg every other day and six i.v. infusions of CYC 600 mg/m^2 every 4 weeks followed by oral AZA 2.5 mg/kg/day, and 23 patients (14 with lcSSc) were randomized to receive matching placebo formulations. Lung function tests were performed after 3, 6, and 12 months, and HRCT was repeated after 1 year. Mean DLCO and FVC were 55% and 82%, respectively, in the patients with lcSSc and 51% and 78% in patients with dcSSc.[20] Analysis of the data showed a non-significant trend towards a between-group difference in the changes in FVC ($p=0.08$).[20] The estimated treatment effect was a 4.19% difference in predicted FVC in favour of the active treatment ($p=0.08$), with a mean unadjusted 2.4% improvement in the active treatment group and a mean 3.0% worsening in the placebo group. Of the 30 patients who underwent HRTC after 1 year (15 from each group), six receiving active treatment (40%) showed some degree of improvement against only three (20%) in the placebo group, but this difference was not statistically significant ($p=0.39$). Although small, this study confirmed the results of the SLS by demonstrating a slight but significant improvement in FVC in patients with SSc-ILD, with no difference in the extent of pulmonary fibrosis revealed by HRTC.[20]

In 2011, Roth et al.[21] analysed the SLS data in order to discover whether any patient subsets are more responsive to CYC by considering treatment, the duration of SSc symptoms, the maximum severity of HRCT reticular changes (MaxFIB score), and the modified Rodnan skin score (mRSS). All of these variables univariately correlated with the baseline to 18-month change in predicted FVC%, and the baseline MaxFIB score, mRSS, and Mahler's Baseline Dyspnoea Index (BDI) proved to be significant independent predictors of the change, i.e. there was a direct relationship between the MaxFIB score and mRSS and the effect of CYC treatment (higher scores corresponded to a greater improvement in FVC%) and an inverse relationship with the BDI (higher scores corresponded to a worse treatment response).[21] On the basis of these findings, the authors used a combination of regression analyses to identify two distinct groups: 53 (49%) patients with a responsive phenotype (a MaxFIB score of ≥3 and an mRSS of ≥23) and 57 patients with a non-responsive phenotype (a MaxFIB score of <3 and an mRSS of <23).[21] When placed into these subsets, the effect of CYC treatment among the responders increased to 9.81% of predicted FVC after 18 months, whereas there was no statistically significant improvement among the non-responders. This study was particularly important because it influenced the clinical management of SSc-ILD patients by distinguishing the patients who benefit more from CYC treatment.[21]

Cyclophosphamide versus azathioprine

One RCT compared AZA and CYC as first-line treatments. The patients receiving AZA showed a significant worsening in FVC and DLCO after 10 months, thus suggesting that AZA is not comparable with CYC as induction therapy, although it may be considered for maintenance treatment.[22]

Cyclophosphamide versus mycophenolate

Given the adverse effects of CYC treatment, particularly in the long term, Tashkin et al.[23] conducted the SLS II in order to compare the efficacy and tolerability of oral CYC and mycophenolate mofetil (MMF).[10] This double-blind, parallel-group randomized trial was conducted at four medical centres in the United States between November 2009 and January 2015. The enrolled patients, who had to have a diagnosis of lcSSc or dcSSc, an FVC of 45–80% of predicted FVC, exertional dyspnoea (a BDI of ≥2), the presence of SSc symptoms for at least 7 years, and any form of ground-glass opacity revealed by HRCT,[23] were randomized to receive oral CYC 2–3 mg/kg for 12 months followed by placebo for another 12 months or MMF 500 mg twice daily for 24 months. The primary aim was to demonstrate the superiority of the effect of MMF on predicted FVC after 2 years and to show that it is safer and better tolerated than CYC in terms of adverse events. The secondary outcome variables included DLCO%, mRSS, and the change from baseline in HRCT lung fibrosis scores. There was no significant between-group difference in FVC% after 24 months (p=0.24), but *post hoc* analyses showed that both treatments significantly increased baseline FVC% (+2.88% in the CYC group and +2.19% in the MMF group). There was also no significant difference in the 24-month mRSS, which decreased in 73.6% of patients treated with CYC and in 71.7% of those treated with MMF. The BDI improved by at least one unit in 59% of the patients receiving CYC and in 47.5% of those receiving MMF.[23] Neither treatment was associated with a change in quantitative HRCT lung fibrosis scores. There were significantly more adverse events in the CYC arm (particularly leukopenia and thrombocytopenia), but there was no between-group difference in the occurrence of anaemia or pneumonia. More CYC-treated patients withdrew from the study and within a significantly shorter time (p=0.019), thus suggesting that MMF is more tolerable. There was no significant between-group difference in FVC% during the study, and interestingly, unlike the patients in SLS I, the patients treated with CYC did not experience a loss of response between months 18 and 24, probably because of the difference in patient selection. Both treatments led to improvements in skin thickness and dyspnoea scores, with no significant difference between the two groups. It is important to note that the only significant differences between the groups were that DLCO% and the DLCO to VA ratio decreased less during MMF treatment. Although it failed to find any significant between-group difference in the primary endpoint (the course of FVC% over 2 years), SLS II was the first trial to show that MMF has a positive effect on SSc-ILD.[23]

On the basis of the SLS II data, Wallace et al.[24] suggested preferring MMF over CYC to treat SSc-ILD and that oral or i.v. CYC for 6–12 months followed by MMF or AZA should be used as the first-line treatment of severe or progressive disease or in the case of a lack of response to MMF.

Cyclophosphamide versus rituximab

Despite the literature favouring CYC treatment, its use is often limited by its side effects and contraindications. One of the most promising new drugs being tested for CTD-ILD is the anti-CD20 monoclonal antibody rituximab (RTX), which is primarily used to treat refractory CTD-ILD. Until recently, no RCTs had been conducted to establish the real effect of RTX treatment on SSc-ILD, but its use was based on case reports and case series that seem to show a beneficial effect on anti-synthetase-associated ILD[25] and SSc-ILD.[26,27] However, a recent EULAR Scleroderma Trials and Research study of patients with severe diffuse SSc and ILD has shown that RTX prevents the decrease in FVC observed in matched controls not receiving RTX.[28]

The still ongoing RECITAL study was started in 2014 with the aims of assessing whether i.v. RTX was more effective and safer than i.v. CYC in treating CTD-ILD and of identifying biomarkers of disease severity, treatment response, and prognosis.[28] It has randomized 116 patients with CTD, MCTD, or SSc and concomitant HRCT-documented ILD to receive CYC 600 mg/m^2 every 4 weeks for 24 weeks or RTX 1000 mg at baseline and after 14 days (with subsequent placebo infusions in order to maintain blindness). The permitted concomitant medications are a stable dose of prednisolone and immunosuppressants

after 24 weeks. The primary outcome measure is the baseline to 24-week change in FVC; the secondary outcome measures include changes in DLCO, the Short Form-36 Health Survey score, the dyspnoea score as measured using the St. George's Respiratory Questionnaire, the global disease activity score, the 6-minute walking test, disease-related mortality, and overall and progression-free survival. It is estimated that the study will be completed in November 2021.[29]

Cappelli et al.[30] analysed the published RCT data demonstrating a significant improvement in FVC in SSc-ILD patients treated with CYC (particularly as induction therapy) and their findings led them to suggest starting CYC induction treatment in the form of intermittent i.v. pulses at a monthly dose of 1 g/m^2 for 6–12 months in order to reduce toxicity. However, there is currently no consensus concerning the dose, duration, or frequency of the pulses.

In the case of refractory ILD, a combination of RTX and CYC or an autologous haematopoietic stem cell transplant can be considered.[22]

Barnes et al.[12] published a Cochrane review of RCTs in which all of the participants had been diagnosed as having CTD-ILD (according to HRCT, lung biopsy, or bronchoalveolar lavage-revealed active alveolitis) and were treated with oral or i.v. CYC. The final meta-analysis included 495 patients who had participated in four randomized, parallel-group trials: three involving adults with SSc (Fibrosing Alveolitis in Scleroderma Trial, SLS I, and SLS II) and one involving adults with SSc, DM/PM, SLE, or RA.[19] The primary outcome of all four trials was the change in lung function as measured in terms of the FVC% and DLCO% of the predicted value. The meta-analysis of the two studies comparing CYC with placebo (for a total of 182 participants) showed a mean baseline to 12-month difference in predicted FVC% of 2.83% (95% CI 0.80–4.87; p=0.006) in favour of CYC and a mean difference in predicted DLCO% of –1.68 (95% CI –4.37 to 1.02; p=0.22).

The meta-analysis of the two trials comparing CYC and MMF showed no significant differences in predicted FVC% after 12 months (mean difference –0.82, 95% CI –3.95 to 2.31; p=0.61) or at the end of the studies (mean difference –0.68, 95% CI –5.44 to 4.08; p=0.78) and no significant difference in predicted DLCO% after 12 months (mean difference –1.41, 95% CI –10.40 to 7.58; p=0.76) or at the end of the studies (mean difference 2.04, 95% CI –1.11 to 5.19; p=0.20). The pooled meta-analysis of adverse events showed significantly more cases of leukopenia (OR 6.86; p<0.00001) and thrombocytopenia (risk difference 0.03; p=0.10) among patients treated with CYC but no significant difference in the risk of pneumonia (OR 1.01; p=0.97) or anaemia (OR 1.63; p=0.30). It was not possible to pool the data for a subgroup analysis based on the severity of the impaired lung function because of the heterogeneity of the trials.

The use of CYC is therefore associated with a small advantage over placebo in terms of FVC% but not in terms of DLCO or mortality. Furthermore, it has no significant impact on lung function or mortality in comparison with MMF but is associated with an increased risk of side effects, particularly leukopenia, neutropenia, thrombocytopenia, and anaemia. However, the conclusions of this review were based on a small number of trials and patients and, as the studies mainly involved SSc patients with ILD, it is unclear whether the findings can be applied to patients with other CTDs.

In conclusion, the crucial role of CYC in treating SSc-ILD is demonstrated by its inclusion in the updated EULAR recommendations for the treatment of SSc[31], particularly in the case of SSc patients with progressive ILD. As in the previous recommendations, the experts did not indicate a standard dose but recommended that both the dose and the duration of treatment should be tailored to the clinical condition and response of individual patients.[30]

Idiopathic inflammatory myositis

Idiopathic inflammatory myositis (IIM) is a rare CTD mainly characterized by inflamed skeletal muscle although extra-muscle involvement is frequent. The prevalence of ILDs among patients with myositis depends on the subtype (PM, DM, antisynthetase syndrome, or clinically amyopathic DM) and screening methods: recent estimates range from 19.9% to 86%.[32]

The most frequent HRCT findings in patients with myositis-related ILDs are bilateral ground-glass opacities and reticulations,[33–36] but they may also include areas of consolidation that suggest cryptogenic organizing pneumonia (COP).[36] Surgical lung biopsies are infrequently indicated but, when conducted, most frequently show the histopathological pattern of NSIP (together with diffuse alveolar damage and COP or UIP).[32]

PM-/DM-related ILDs may precede, accompany, or follow extra-pulmonary manifestations,[37] and rapidly progressive ILD with acute respiratory failure may occur, particularly in patients with melanoma differentiation-associated protein 5 antibodies and clinically amyopathic DM.[38] The risk factors involved are an age of >45 years, joint involvement, and (particularly) the presence of aminoacyl-tRNA synthetase antibodies.[37,39] Some patients have antisynthetase syndrome, which consists of various combinations of fever, arthralgia, Raynaud's phenomenon, and 'mechanic's hands' (i.e. dry, rough, and fissured skin, especially on the thenar side of the forefinger and finger tips), ILD, and anti-aminoacyl-tRNA synthetase antibodies (anti-Jo-1, anti-EJ, anti-OJ, anti-PL7, and anti-PL12).[38,39] The 5-year survival of PM/DM-ILD patients is 60–80%.[40]

There have been no clinical trials involving IIM-ILD patients but data from case series and individual case reports suggest using high-dose GCs as first-line treatment, with the addition of an immunosuppressant such as AZA, MMF, and/or CYC.[41] Severe and rapidly progressive cases have been treated with i.v. CYC and high-dose methylprednisolone.[41]

Treatment with CYC has been successful in the case of rapidly progressive or refractory PM/DM,[42] with maintenance treatment with MMF or a calcineurin inhibitor after 6–12 months.

Sjögren's syndrome

Between 3% and 11% of patients with primary SS-develop ILDs, which may lead to life-threatening complications such as secondary PAH and respiratory failure;[43–45] they have has also been found to be responsible for mortality rates of 42.9–90% in small patient series.[46,47] It was initially thought that ILD develops at the same time or after SS,[48,49] but it has more recently been reported that it develops before SS in 25.5% of cases.[50]

Lymphocytic interstitial pneumonia (LIP) used to be considered the most characteristic histopathological finding (i.e. benign, polyclonal, diffuse, or local proliferation of mature B or T cells)[49] and was believed to be relatively responsive to GCs,[49] although CYC, AZA, and chlorambucil have also been used with mixed results.[50] However, it has now been shown that the most prevalent pattern is NSIP[51] and a systemic dose of GCs of 0.5–1 mg/kg/day is normally combined with CYC or AZA, although it has not been shown that this treatment is effective.[51]

Mixed connective tissue disease

Lung complications, which frequently occur in patients with MCTD, are associated with higher mortality rates:[54] up to 33% of patients have reduced DLCO levels and about 50% have signs of restrictive pulmonary function.[52] The most frequent radiological abnormalities are ground-glass opacities and predominantly lower septal thickening, which are observed in 20–60% of cases.[53] Patients are usually treated with GCs, but this is not supported by much concrete evidence. Immunosuppressants can also be considered.[54]

Systemic lupus erythematosus

ILDs seem to be less frequent and severe in patients with SLE, who often have no respiratory symptoms but frequently show PFT and HRCT abnormalities, and their lung complications can significantly worsen their prognosis.[55,56] Diffuse ILD or chronic pneumonitis are observed in 3–11% of patients with SLE. The usual histopathological pattern is NSIP but COP, LIP, and UIP are also observed in some cases.[55,56] The recommended treatment is high-dose methylprednisolone (1 g/day for 72 h), followed by oral corticosteroids and possibly i.v. CYC.

Conclusion

It is now widely acknowledged that ILDs are frequent and serious complications of CTDs and rheumatic diseases but estimates of their prevalence vary widely and depend on study designs and study populations as well as on the way in which the diseases are defined. ILDs are more frequent in patients with SSc, RA, or IIM: the most frequent CTD-ILD is NSIP, but RA patients more frequently develop UIP, which may shorten their survival in comparison with that of patients with other CTDs.[1] Managing CTD-ILDs is challenging because the diseases are heterogeneous, there is a lack of robust treatment data, and there are only a few well-defined outcome measures. Treatment choices are often made based on functional or radiographic progression and on the assessment of factors such as age and comorbidities because a considerable percentage of patients have mild disease and do not progress.

On the basis of RCT findings, administering CYC for 1 year is an effective way of treating SSc-ILDs but, given the short duration of the effect, this treatment should be considered cautiously and based on its risk-to-benefit ratio in individual patients because it is sometimes associated with significant adverse events such as a higher risk of infections, infertility, and haemorrhagic cystitis. The various strategies that have been proposed in order to avoid adverse events include administering i.v. rather than oral CYC and using CYC for induction purposes followed by MMF and AZA. The use of MMF and RTX as first-line treatment has beneficial effects, but this is not true of AZA. Finally, EULAR recommends that CYC should be considered, particularly in the case of patients with SSc with progressive ILD, but it is still unclear whether this also applies to other CTD-ILDs.

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