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Connective tissue disease associated interstitial pneumonia: a challenge for both rheumatologists and pulmonologists

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Abstract. Interstitial lung disease (ILD) can be either idiopathic, the result of exposure or may be associated with extrapulmonary diseases. Among the latter, connective tissue diseases (CTDs) make up the largest part. The identification, follow-up and treatment of CTD-associated ILD (CTD-ILD) are a challenge for every physician as ILD can occur before, during and after the diagnosis of CTD. Early detection of pulmonary involvement is an essential task for the treating rheumatologist and recognition of the underlying CTD can pose a challenge for the treating pulmonologist. Multidisciplinary engagement towards the patient is therefore indispensable for optimal clinical care. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 326-335)*

Key words: connective tissue disease, interstitial lung disease, collagen vascular disease, pulmonary fibrosis, diagnosis, evaluation, treatment

Introduction

The connective tissue diseases (CTDs) refer to a group of systemic rheumatologic illnesses characterised by autoimmunity and autoimmune-mediated organ dysfunction. The CTDs include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), primary Sjögren's syndrome (pSS) and mixed connective tissue disease (MCTD). Involvement of the respiratory system, particularly interstitial lung disease (ILD), is common and an important contributor to morbidity and mortality. The term ILD is used to describe a heterogeneous group of parenchymal lung disorders that share common radiologic, pathologic and clinical manifestations. ILD is characterized by a varying combination of inflammation and fibrosis involving the space between epithelial and endothelial membranes (1). CTD-related ILD (CTD-ILD) can precede, occur together or follow the appearance of CTD-features. We can distinguish ILD in the context of a known CTD, CTD in the context of pre-existing ILD, and ILD with features of CTD which do not meet the predefined classification criteria (2-4).

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1. ILD in the context of pre-existing CTD

Prevalence and prognosis

RA is the most common of the CTDs mentioned above. ILD is a serious extra-articular manifestation of RA, and the leading cause of death in RA-patients (5). Approximately 10% of patients with RA have clinical evident ILD, and an additional 30% have subclinical ILD (6). RA-ILD patients with a UIP pattern on HRCT have worsened sur-

vival compared to those without (median survival 3,2 years versus 6,6 years) (7). Pulmonary involvement is a common finding in SSc which presents either as ILD or pulmonary arterial hypertension and constitutes the leading cause of disease-related mortality. Clinically significant disease occurs in an estimated 40% of patients and with the use of HRCT ILD is detected in 65% of all patients (8). The median survival of patients with SSc-ILD is 5 to 8 years (9). ILD is a frequently seen complication in PM/DM and clinical relevant ILD seems to occur in almost 30% of patients. ILD is the hallmark of pulmonary involvement in the idiopathic inflammatory myopathies (IIMs), resulting in estimated excess mortality of 50% (10). Clinically significant ILD is estimated to occur in 11% of patients with Sjögren's syndrome. Many patients are asymptomatic and lung involvement is mild and only slowly progressive. Five-year survival for patients with pSS-ILD is 84% (9). Pulmonary involvement in SLE can affect the pleura, pulmonary vasculature and parenchyma (11). With a reported prevalence of 3% to 13%, the prevalence of ILD appears to be lower in SLE than in other CTDs. However, subclinical disease is likely common, based on HRCT studies that estimate the prevalence of ILD at 38% among SLE-patients without previously diagnosed lung disease (8). MCTD shares similar clinical features with the different CTDs, so any of their pulmonary manifestations may be present. Patients with MCTD do not meet criteria for another CTD, but long term follow-up shows that most patients develop one of the more recognized CTD entities -usually SSc- over the next 5 years (12, 13).

Radiologic patterns

Thoracic high-resolution computed tomography (HRCT) imaging plays a central role in the evaluation of ILD by providing detailed information on the pattern, distribution, and extent of ILD. The use of HRCT also gives additional information about disease severity and the presence of extraparenchymal abnormalities. The most common patterns are those that reflect the underlying histopathology of nonspecific pneumonia (NSIP) and usual interstitial pneumonia (UIP). To a lesser extent the patterns of organizing pneumonia (OP), diffuse alveolar damage (DAD) and lymphocytic interstitial pneumonia (LIP) can be identified (4). HRCT characteristically reveals increased reticular markings, traction bronchiectasis and minimal honeycombing, with basilar predominance when it is consistent with an NSIP pattern. The distribution of ground-glass opacities is often symmetric with involvement of the middle and lower zones or the lower zones alone. In contrast, an UIP pattern is characterized by patchy reticulo-nodular opacities associated with traction bronchiectasis and honeycombing with a predominantly basal and peripheral reticular pattern (14, 15). Ground-glass opacities are more uncommon, and if present less extensive than the reticulation. Histologically, NSIP is characterized by varying degrees of inflammation and fibrosis, with the majority of patients showing a prominent inflammatory process. The UIP pattern of fibrosis is histologically characterised by spatial heterogeneity, which refers to a patchy distribution of dense parenchymal scar (fibroblast foci) alternating with areas of less affected or normal parenchyma, and by temporal heterogeneity, which reflects different stages in the evolution of fibrosis, a combination of old and active lesions (1). The NSIP pattern is the most frequent ILD pattern seen in the setting of SSc, while the UIP pattern appears to be more common in RA. Overlapping patterns are not unusual and can be considered almost routine in disorders such as PM/DM and SLE. More unusual patterns, such as LIP may especially occur in Sjögren's syndrome (16).

Auto-antibodies

Patients with RA present circulating antibodies, mainly rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) (5). Among patients with RA-ILD, RF and anti-CCP antibodies are positive in 89% and 94%, respectively. By comparison, RF and anti-CCP antibodies are present in 58% and 55% of RA-controls, respectively (17). The combination of clinical risk factors (older age, male sex, history of smoking) and auto-antibodies (RF, anti-CCP) is strongly associated to the presence of clinically evident and subclinical RA-ILD. Pulmonary involvement seen in SSc is associated with specific auto-antibodies, for example anti-topoisomerase I (anti-Scl-70). In contrast, anti-centromere antibodies (ACA) appear to be protective, although patients with limited systemic sclerosis are not excluded from developing ILD (11). Substantial heterogeneity exist within the spectrum of

the IIMs and is partly related to the presence of various auto-antibodies, encompassing anti-synthetase, anti-Mi2 or anti-CADM-140 and anti-PM/Scl. The anti-synthetase syndrome, characterized by the clinical picture of Raynaud, myositis, arthritis, ILD and mechanic's hands is associated with the presence of anti-aminoacyl tRNA synthetase antibodies (anti-ARS), of which anti-Jo-1 is the most prevalent. Various other anti-ARS-antibodies have been identified so far, including PL-7, PL-12, EJ, OJ, KS, YRS and Zo. Jo-1 positivity is found in approximately 20% of myositis patients (18). Anti-PL-7 and anti-PL-12 are less frequently found, whereas the remaining are exceedingly rare. In ARS, incidence rates of ILD as high as 80-95% have been reported (19). Nuclear helicase-ATPase Mi2 is found exclusively in dermatomyositis, and is associated with a paucity of extramuscular features, better prognosis and better response to immunosuppressive therapy. Clinically amyopathic dermatomyositis (CADM) is characterized by the presence of anti-MDA5 antibodies and is usually associated with rapidly progressive ILD. The occurrence of myositis-associated auto-antibodies, such as anti-PM/Scl is less frequently associated with the presence of ILD. Anti-PM/Scl auto-antibodies have been found in 17% of patients with IIM–limited SSc overlap syndrome (10) pSS is characterized by the production of antibodies against Ro (anti-SSA) and/or La (anti-SSB) ribonucleoproteins. SSA and SSB are non-specific antibodies, therefore their presence does not contribute to the establishment of a diagnosis (12). In most patients with SLE anti-double-stranded DNA (dsDNA), anti-Smith auto-antibodies, as well as several other auto-antibodies are present (8). MCTD is an overlapping CTD sharing clinical features with SLE, PM/DM, RA and SSc in the presence of high titer anti-U1-ribonucleoprotein (anti-U1-RNP) antibodies (13). Anti-U1-RNP is not specific for MCTD but high titers of anti-U1-RNP do characterize MCTD and are a condition sine qua non for MCTD diagnosis (4).

Evaluation of ILD

Symptom assessment and physical examination

Patients with CTD should be asked about the occurrence of dyspnea at every clinical visit, since dyspnea is typically the first and predominant symptom of ILD. Other symptoms commonly reported in patients with CTD-ILD include cough, sputum production and fatigue. All patients with CTD should be subjected to a thorough physical examination for features of ILD at baseline and this should be repeated at regular follow-up visits (20-22).

Pulmonary function tests

Pulmonary function tests (PFTs) are used to screen patients with CTD for ILD, to support new diagnosis in patients with suspected CTD-ILD, or to monitor disease activity and progression in patients with an established CTD-ILD diagnosis. PFTs should be performed in all patients with unexplained symptoms of physical examination findings that are consistent with ILD. However, PFTs can be normal in early ILD, and thus the presence of normal physiology does not rule out mild ILD. A normal PFT can also indicate the presence of ILD if previous measurements showed supranormal values, illustrating the importance of comparison to previous tests. Reduced diffusion capacity of the lung for carbon monoxide (DLCO) is often the first physiologic manifestation of ILD, but many CTDs are at risk for pulmonary arterial hypertension which is also characterised by a decreased DLCO. More advanced ILD is characterized by a restrictive pattern with proportionately reduced flow rates (forced vital capacity [FVC]) and reduced lung volumes (total lung capacity [TLC]). The forced expiratory volume in one second [ESW] usually remains preserved until the final stage of ILD (23). Baseline FVC is of unclear predictive value in ILD, whereas DLCO is more reliably predictive of survival at baseline, and a threshold of approximately 40% of the predicted value has been associated with an increased risk of mortality (24). Once a diagnosis of ILD is established, repeated testing at regular intervals should be performed to quantify the severity of the impairment, to assess for disease progression, and to monitor the response to treatment. According to ATS/ERS guidelines a 10% decline in FVC or a 15% decline in DLCO is considered clinically important and should be a reasonable threshold to indicate worsening ILD in patients with CTD-ILD and to plan further investigation, such as HRCT (16, 23-26). However, recent literature suggests a 5% difference in FVC to be clinically meaningful in ILD

(27). Interpretation of PFTs may be especially challenging in PM/DM because of het potential coexistence of respiratory muscle weakness, which impairs DLCO (10). Evidence regarding how often patients with CTD with existing ILD should be monitored for disease progression is lacking. In many experienced centers patients with existing ILD are typically evaluated every three to four months, depending on the overall prognosis and risks of ILD progression (Figures 1 and 2).

Functional assessment

The six-minute-walk-distance (6MWD) is a standardized tool that provides a simple measurement of functional capacity and may add prognostic

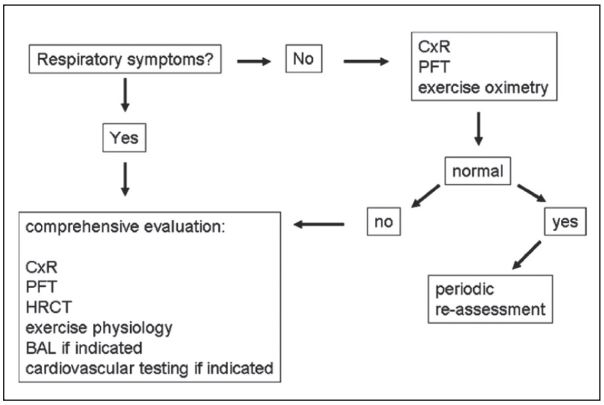

Fig. 2. Algorithm for the investigation of lung disease in CTD patients. Adapted from "Diffuse lung disease: A practical approach to connective tissue disease-associated lung disease," by Fischer A and du Bois RM. Springer Science 2012, 217-237

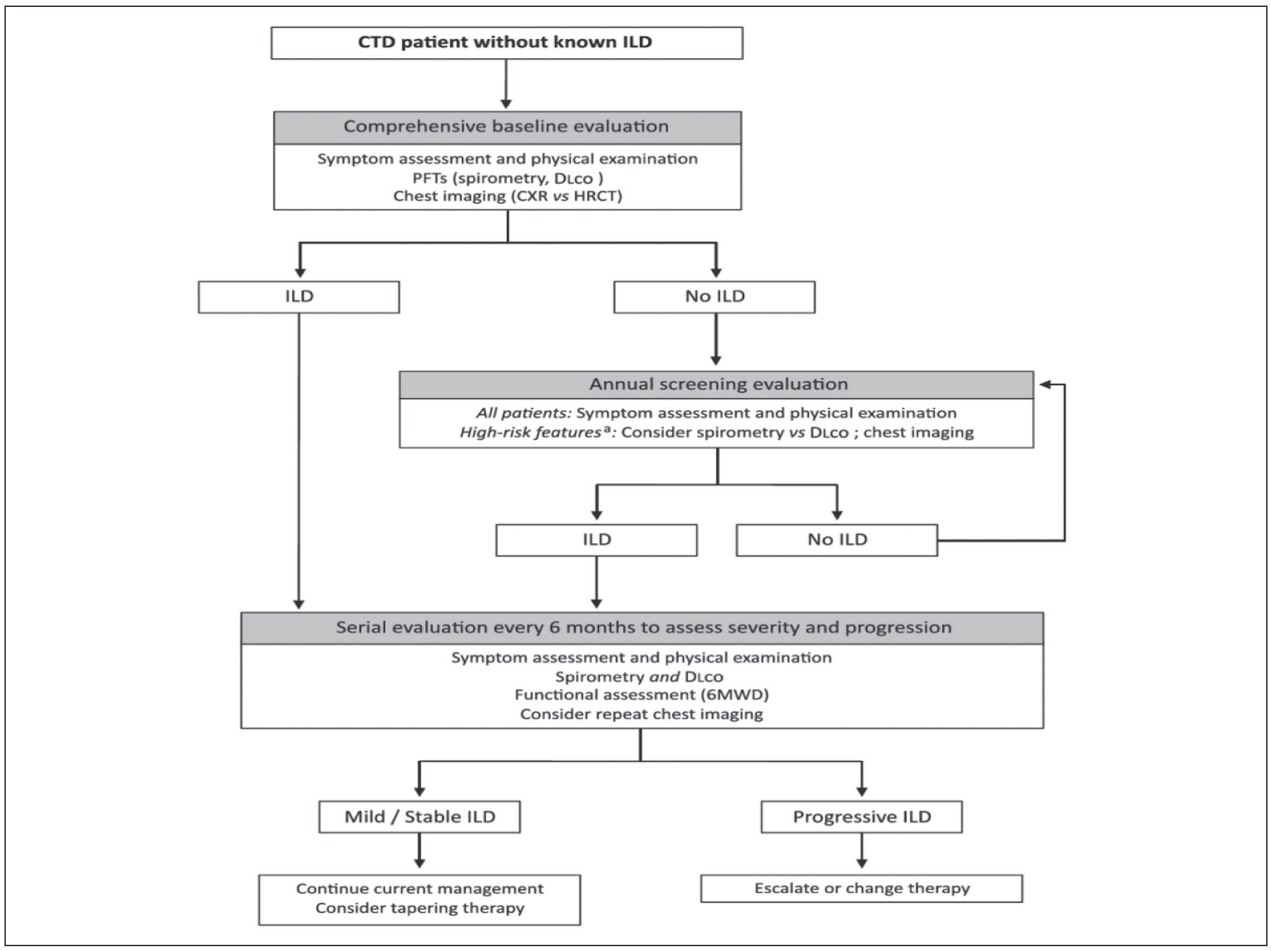

Fig. 1. Proposed algorithm for the evaluation of ILD in patients with CTD. High-risk features can include demographic features (e.g. increased age, male sex), CTD subtype, auto-antibody status and others. Adapted from "Determining respiratory impairment in connective tissue disease-associated interstitial lung disease," by Assayag D and Ryerson CJ. Rheum Dis Clin N Am 2015, 41: 213-223

information beyond the standard PFTs. The major limitation of the 6MWD in CTD-ILD is the lack of organ specificity, because abnormalities can also be caused by cardiac disease, pulmonary arterial hypertension or the presence of musculoskeletal disease. Despite its limitations in identifying ILD in patients with CTD, the 6MWD can be used to monitor disease progression and provide prognostic information in patients with established CTD-ILD. Therefore, a regular assessment of the 6MWD is suggested (21, 25, 28). Cardiopulmonary exercise testing (CPET) can be useful in CTD-ILD to determine if the dyspnea is primarily caused by ILD, pulmonary vascular disease, cardiac disease or another aetiology (21). Reduced breathing reserve as a measure for poor ventilatory capacity and impaired gas exchange can be seen in ILD (12).

Chest imaging

Historically, plain chest radiography has been used to detect and monitor ILD because it is relatively cheap, readily available and associated with a low radiation burden. However, chest radiography lacks sensitivity and specificity for ILD in a screening setting, and its interpretation is often difficult. In the meantime, chest radiography may still be useful in the initial evaluation of pulmonary symptoms because it can identify CTD-associated pulmonary manifestations (e.g., pleural effusions or pneumonia) (15). HRCT can be used to reliably diagnose or exclude ILD. However, it is costly and associated with non-trivial radiation exposure that increases the risk of malignancy. Another drawback essential to clinicians is that, due to its sensitivity, subclinical abnormalities are often present that do not necessarily evolve to clinically significant ILD. For these reasons HRCT is not routinely used as a serial screening test in asymptomatic patients. On the other hand, in patients with suspected ILD the use of HRCT of the chest is essential, whereas plain chest radiography is not useful in diagnosing ILD due to lack of sensitivity. HRCT can also guide management by suggesting the ILD subtype, and therefore provide prognostic information (29). The extent of fibrosis on HRCT also suggests a poor prognosis in multiple CTD-ILD subtypes, and can provide further evidence of stability or worsening in patients with unclear evidence of progression (15, 21, 30-32). It is shown that an increasing extent of honey-combing and severity of traction bronchiectasis is independently associated with increasing mortality in CTD-ILD (33). HRCT represents the golden standard for diagnosing ILD. Even though cumulative effects of ionising radiation due to serial testing in follow-up are linked to an increased risk of cancer, the recent introduction of low-dose CT mitigates this issue (34). Whereas wide-scale screening with HRCT imaging is not advocated yet, the importance of clinical vigilance is highlighted, while maintaining a low threshold to proceed with full pulmonary evaluation given the potentially devastating manifestations of lung diseases that can occur in all CTDs (4).

Bronchoalveolar lavage and lung biopsy

Bronchoalveolar lavage (BAL) allows for investigation of the lower respiratory tract through sampling of (a)cellular components from the bronchoalveolar lung units. BAL fluid analysis may be helpful in evaluating the activity of the processes involved in the development of CTD-ILD, and in identifying patients at risk of progressive lung fibrosis (3, 35). The majority of patients with an acute onset of ILD will also undergo BAL to evaluate for alveolar hemorrhage, malignancy, and opportunistic or atypical infection (36). BAL also has a role in the diagnostic work-up of patients who cannot, or will not agree to, be subjected to more invasive procedures (37). Transbronchial lung biopsy (TBLB) is performed only when no confident diagnosis can be made based on other available information and when a specific histological diagnosis is thought to add important value to prognosis or therapy. Based on small sample size, potential sampling error and crush artefacts, TBLB is of limited value in the evaluation of CTD-ILD, but may be diagnostic in more airway-centric complications such as bronchiolitis, hypersensitivity pneumonitis, sarcoidosis or malignancy (1, 3, 35). The introduction of less invasive techniques such as transbronchial cryobiopsy (TBCB) show great promise to clinical practice, but more studies should be performed to evaluate the reliability of TBCB as a diagnostic tool (38). As a result of the diagnostic power of HRCT, a surgical lung biopsy (SLB) does not provide additional information when the HRCT pattern is consistent with the clinical features of a specific CTD. Moreover, the relation between histo-

pathologic pattern and clinical outcome or prognosis in patients with CTD is less obvious than what is reported for idiopathic interstitial pneumonia (IIP). SLB should only be considered in CTD-ILD when the HRCT pattern is inconsistent with, of atypical for the specific CTD presumed, or whenever clinical disease behaviour differs from what is expected (39).

New developments: MRI and FDG-PET

Pulmonary functional MRI was suggested as a new approach for assessment in various pulmonary diseases, offering the opportunity of radiation-free imaging. With oxygen-enhanced MRI, the percentage of oxygen-enhanced pixels strongly correlated with measurements of gas transfer in CTD-ILD-patients (40). Ohno et al. showed that the mean T2 values for normal and CTD-subjects were significantly different and it showed significant correlations with changes in PFT values in CTD-patients with ILD (41). Uehara et al. demonstrated that deep inspiratory breath hold 18-F FDG-PET/CT sensitively illustrates active ILD-lesions in CTD-patients. Both intensity and distribution of FDG-signals correlated with disease activity, regardless of the underlying CTD and CT pattern. FDG-signals reduce with the clinical improvement in response to medical therapy, even when abnormal CT findings remain after resolving inflammation. This non-invasive imaging modality is useful for assessing and monitoring CTD-ILD, especially in patients with serious ILD and unremarkable interval changes in the follow-up CT scans (42). The findings of Owada et al. indicate that the routine use of FDG-PET in patients with PM/DM had limited value for the detection of myositis and ILD because of its low sensitivity. However, it might be a good modality for screening for malignancy associated with PM/DM (43). The major disadvantages of MRI and FDG-PET/CT are the high cost and the low availability. Large prospective studies are warranted to determine the real significance of these new techniques in the clinical setting.

2. Identifying CTD in patients with ILD

Since ILD can precede the development of other CTD features, awareness is also warranted in routine pneumology clinical care. Physical examination findings provide important clues for diagnosis of an underlying rheumatic condition. Symptoms and examination features that commonly are associated with an underlying CTD include joint and muscle symptoms, Raynaud's syndrome, gastrointestinal symptoms, sicca symptoms, skin manifestations, chest pain or eye abnormalities (13). Laboratory screening is used to decide if further CTD-evaluation is needed. The current standard practice is to draw antinuclear antibodies (ANA) with pattern and titer, and RF and anti-CCP, and if any are positive, a rheumatologic evaluation is requested. This approach is less than ideal for a number of reasons. Foremost, ANA and RF are poor screening tests: they have low specificity –particularly when present in low titer– and can be seen in healthy individuals, as well as in elderly where the incidence of ILD is higher. Furthermore, in cases with negative ANA and RF occult CTD can be missed. It is important to take note of the pattern of immunofluorescence when the ANA is positive, as the nucleolar and centromere staining ANA pattern in patients with ILD suggests SSc spectrum of disease. More specific antibodies do serve as integral components in the assessment for CTD-ILD (4). Since the preceding of pulmonary symptoms frequently occurs in patients with IIMs, a screening panel including myositis antibodies should be considered in the near future. Paradoxically, the detection of autoantibodies often raises more questions and may not clarify classification, due to shortcomings of existing rheumatologic classification criteria (44, 45).

3. Interstitial pneumonia with autoimmune features (IPAF)

The idiopathic interstitial pneumonias (IIPs) are diffuse inflammatory and/or fibrotic lung disorders that are grouped together based on similar clinical, radiologic and histopathologic findings. The diagnosis of IIP requires the exclusion of known causes of interstitial pneumonia, such as environmental exposures, medication toxicity or CTD. Many patients with an IIP have clinical features that suggest an underlying autoimmune process but do not meet established criteria for a CTD. These patients have formerly been labelled undifferentiated CTD-ILD (uCTD-ILD), lung-dominant CTD or autoimmune-featured ILD. Recognition that the understanding of this clinical

entity might benefit from an improved classification system with uniform diagnostic criteria, led to the introduction of a novel entity termed interstitial pneumonia with autoimmune features (IPAF) (46, 47). This new classification system incorporates criteria based on the combination of features from three domains: a clinical domain consisting of specific extra-thoracic features, a serologic domain consisting of auto-antibodies, and a morphologic domain consisting of specific chest imaging, histopathologic or pulmonary physiologic features. In clinical practice it is recommended to have the expert-opinion of a multidisciplinary team for the assessment and management of all patients with ILD (48). IPAF is defined, but to date there are no recommendations for its treatment (49, 50). It remains to be seen whether application of the IPAF criteria can identify patients who may benefit from immunosuppressive therapy, as is the case in CTD-ILD (46).

Prognosis and treatment

Several risk factors for ILD have been identified in patients with CTD, but the clinical utility of these is unknown. Demographic predictors of CTD-ILD include older age, smoking and male sex. The presence of certain autoantibodies is also associated with increased risk of ILD. Severity of lung function impairment is consistently associated with increased mortality in RA-ILD and SSc-ILD. Despite these associations there is currently no evidence that patients with high-risk clinical features should undergo more rigorous serial screening for ILD. Additional studies are therefore needed to validate predictors of ILD onset and to determine the role of these predictors in clinical practice (21). Pulmonary disease is the leading cause of mortality in patients with SSc, but also in RA ILD is an important factor to determine survival, especially in those patients with a UIP pattern on HRCT/biopsy. Accurate prognostic evaluation allows the selection of higher risk patients who may benefit from treatment (8). The most difficult clinical decision in CTD-ILD is to determine when treatment should be initiated and when meticulous observation without intervention is appropriate. This problem has been confronted especially in SSc-ILD, although it seems probable that the same principles apply to other forms of CTD-ILD. In overtly severe ILD in the context of any CTD, the decision to treat is generally straightforward. However, in the much larger group of CTD-ILD with milder disease, a reliable means of identifying intrinsically progressive ILD would provide a rationale for early intervention. The decision to treat CTD-ILD is then based on whether the patient is clinically impaired by the ILD, whether the ILD is progressive by symptoms, physiology and/or imaging, and what extrathoracic features require therapy. Importantly, no overall algorithm integrating these factors has been validated so far. Goh et al. proposed a simple staging system for SSc-ILD as limited or extensive disease integrating HRCT appearance (cut-off 20% fibrosis) and FVC estimation (cut-off 70%), that provides powerful prognostic information (31). In all cases of CTD-ILD, disease monitoring, choice of therapy and longitudinal monitoring of treatment response are complex, but it can be optimized by cross-specialty collaboration (4). The clinical course and therapeutic response vary depending on ILD aetiology. Patients with CTD-ILD are prone to have a more favourable clinical outcome when compared to IPF, thus therapy strategies should be adopted with caution, and by means they should not be extrapolated from one CTD to another (46).

Immunosuppression

Historically, the management of CTD-ILD has mostly consisted of the suppression of inflammation with corticosteroids (CS) or immunosuppressive therapy (26). In general, the more fibrotic forms of ILD (UIP and fibrotic NSIP) tend to be less corticosteroid responsive when compared with more cellular forms of ILD (cellular NSIP, OP, LIP) (4). Induction therapy requires high dosing of CS along with short-term use of a more potent steroid-sparing agent, such as cyclophosphamide (CYC). Initial therapy is followed by a maintenance therapy with a less toxic agent, such as azathioprine (AZA) or mycophenolate mofetil (MMF) in combination with a gradual decrease in dose of CS (51).

Anti-fibrotic therapy

Given the magnitude of the impact of fibrosis on mortality the pace of development of effective anti-fibrotic drugs has been disappointing, until recently. In

2014, the Food and Drug Administration approved two new drugs, nintedanib and pirfenidone, for the treatment of IPF (52). Nintedanib is an intracellular inhibitor of several tyrosine kinases that targets multiple growth factor receptors implicated in the pathogenesis of fibrosis. The benefit of nintedanib on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality and a lower value of significant adverse effects marks a turning point in treatment options of ILD. Pirfenidone is an anti-fibrotic drug with pleiotropic effects, but its mechanisms of action remain unclear so far. As nintedanib, pirfenidone shows promising benefits on patient-important outcomes (53). These promising clinical effects in IPF hold great promise for similar anti-fibrotic effects in CTD-ILD, as is the case in a small case series of 5 SSc-ILD patients being treated with pirfenidone (54). Gastrointestinal and skin problems are the most frequent adverse events with pirfenidone, and gastrointestinal adverse effects (predominantly diarrhoea) are most common with nintedanib. Although it is hoped that the lower decline in FVC will be maintained over extended periods of time, long-term studies are needed to assess whether these drugs will slow the disease process for longer duration and yield a true survival benefit. In addition, the expenses of dispensing these drug need to be taken into consideration while acknowledging that the costs are variable worldwide and are dictated by factors beyond scientific merits (55-58). Until more data become available from well-designed randomized controlled-trials, the off-label use of anti-fibrotics in CTD-ILD is not supported.

Biological agents

The continuously increasing understanding of the role of pro-inflammatory cytokines in the molecular pathways of inflammation and autoimmunity led to the discovery of biological agents, such as TNFα receptor inhibitor etanercept and the anti-TNF monoclonal antibodies infliximab, adalimumab, golimumab and certolizumab, as well as the IL-1 receptor antagonist anakinra and the anti-IL-6 receptor monoclonal antibody tocilizumab (59). The latter proving to establish a lesser decline in predicted FVC compared to the placebo group in a recent phase 2 clinical trial (60). The influence of anti-TNF therapy in established ILD in patients with RA is not clear and some reports even mention worsening of existing ILD disease (61). The role of B-cell depleting anti-CD20 antibody rituximab remains to be defined, but recent studies suggest rituximab may be an effective agent as rescue therapy or in severe, refractory CTD-ILD (62, 63). Together with anti-T-cell agent abatacept, all the drugs above have been used off-label in autoimmune disorders with various success (59). There are many new therapeutics which are attractive candidates based largely on in vitro evidence from laboratory studies and supportive animal experiment findings, although they have not been appropriately tested in controlled clinical trials. It is becoming apparent that fibrotic diseases need the use of multiple drugs to affect different pathways. This is due to the fact that the pathogenic mechanisms in fibrotic diseases consist of complex networks of multiple and often redundant pathways and blocking a single node will usually not be sufficient or effective (64).

Adjunctive therapy

In addition to immunosuppressive therapies, patients with CTD-ILD should receive supportive care measures that should include supplemental oxygen, pulmonary rehabilitation therapy and appropriate vaccination, consisting of yearly influenza vaccination and periodic vaccination against pneumococcal pneumonia. Furthermore, patients on immunosuppressive therapy should receive prophylaxis against Pneumocystis Jirovecii. Additional smoking cessation is a fundamental component of treating any chronic lung disease and CTD-ILD is no different (51, 52).

Conclusion

ILD is a common complication of CTD and is associated with significantly increased morbidity and mortality. Moreover, ILD is often one of the most important causes of death in this particular patient population. The evaluation of ILD in CTD-patients is a complex task considering the heterogeneity of CTDs, the various types and degrees of severity of ILD and because ILD can be identified at any point in time in these patients. In view of the highly variable clinical course of CTD-ILD and significant tox-

icity of immunosuppressive therapies used for treatment of CTD-ILD, identification of patients with a poor prognosis is of key importance, ideally before irreversible damage develops. A thorough and multidisciplinary evaluation is necessary when a CTD-patient develops ILD. To determine whether an ILD is associated with a known CTD demands the exclusion of alternative aetiologies and extensive knowledge of CTDs and ILD. Special attention must be paid to the demographic data, medical history, physical examination, serologic profile and radiologic and histopathologic findings. Recommendations for the evaluation and management of CTD-ILD are primarily based on expert opinion that is derived from clinical experience or extrapolation from evidence in other ILDs. Despite impressive recent advances, the management of patients with CTD-ILD remains unsatisfactory. The high disease burden together with the lack of data on existing anti-fibrotic treatments in other diseases defines a high unmet need for novel therapeutic strategies. More research is needed to better understand the complex intersect of lung disease with systemic autoimmunity. Take note that new studies are on their way and more information will be available in the near future.

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References

1. Buzan MTA, Pop CM. State of the art in the diagnosis and management of interstitial lung disease. Clujul Med 2015; 88 (2): 116-123.
2. Tsuchiya Y, Fischer A, Solomon JJ, Lynch DA. Connective tissue disease related thoracic disease. Clin Chest Med 2015; 36: 283-297.
3. Fischer A, Lee JS, Cottin V. Interstitial lung disease evaluation: detecting connective tissue disease. Respiration 2015; 90: 177-184.
4. Fischer A, du Bois RM. Diffuse lung disease: A practical approach to connective tissue disease-associated lung disease. Springer Science 2012: 217-237.
5. Papiris SA, Manali ED, Kolilebas L, Kagouridis K, Maniati M, Borie R et al. Investigation of lung involvement in connective tissue disorders. Respiration 2015; 90: 2-24.
6. Doyle TJ, Patel AS, Hatabu H, Nishino M, Wu G, Osorio JC et al. Detection of rheumatoid-arthritis-interstitial lung disease is enhanced by serum biomarkers. Am J Respir Crit Care 2015; 191 (21): 1403-1412.
7. Kim EJ, Ellickers BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010; 35 (6): 1322-1328.
8. Antin-Ozerkis D, Rubinowitz A, Evans J, Homer RJ, Matthay RA. Interstitial lung disease in the connective tissue diseases. Clin Chest Med 2012; 33: 123-149.
9. Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. Chest 2013; 143 (3): 814-824.
10. Lega JC, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V. Idiopathic inflammatory myopathies and the lung. Eur Respir Rev 2015; 24: 216-238.
11. Olson AL, Brown KK, Fischer A. Connective tissue disease-associated lung disease. Immunolog Allergy Clin N Am 2012; 32: 513-536.
12. Mira-Avendano I, Abril A. Pulmonary manifestations of Sjögren syndrome, systemic lupus erythematosus and mixed connective tissue disease. Rheum Dis Clin N Am 2015; 41: 263-277.
13. Strange C, Highland KB. Interstitial lung disease in the patient who has connective tissue disease. Clin Chest Med 2004; 25: 549-559.
14. Castelino FV, Varga J. Interstitial lung disease in connective tissue diseases: evolving concepts of pathogenesis and management. Arthritis Res Ther 2010; 12 (4): 213.
15. Woodhead F, Wells AU, Desai SR. Pulmonary complications of connective tissue diseases. Clin Chest Med 2008; 29: 149-164.
16. Fischer A, Brown K. Pulmonary manifestations of rheumatic disease: A comprehensive guide. Evaluation of lung disease in patients with connective tissue disease. Springer Science 2014: 13-23.
17. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiologic and radiologic characteristics – a large multicentre UK study. Rheumatology 2014; 53 (9): 1676-1682.
18. Ingegnoli F, Lubatti C, Ingegnoli A, Boracchi P, Zeni S, Meroni PR. Interstitial lung disease outcomes by high-resolution computed tomography (HRCT) in Anti-Jo1 antibody-positive polymyositis patients: a single centre study and review of the literature. Autoimmunity reviews 2012; 11: 335-340.
19. Lega JC, Cottin V, Fabien N, Thivolet-Béjui F, Cordier JF. Interstitial lung disease associated with anti-PM/Scl or anti-aminoacyl-tRNA synthetase autoantibodies: a similar condition? J Rheumatol 2010; 37 (5): 1000-1009.
20. Swigris JJ, Yorke J, Sprunger DB, Swearingen C, Pincus T, du Bois RM et al. Assessing dyspnea and its impact on patients with connective tissue disease-related interstitial lung disease. Respir Med 2010; 104: 1350-1355.
21. Assayag D, Ryerson CJ. Determining respiratory impairment in connective tissue disease-associated interstitial lung disease. Rheum Dis Clin N Am 2015; 41: 213-223.
22. Cottin V, Cordier JF. Velcro crackles: the for early diagnosis of idiopathic pulmonary fibrosis? Eur Respir J 2012; 40: 519-521.
23. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. The Lancet 2012; 380: 689-698.
24. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R et al. ATS/ERS task force: Interpretative strategies for lung function tests. Eur Resp J 2005; 26: 948-968.
25. Deutschle K, Weinert K, Becker MO, Becker MO, Huscher D, Riemekasten G. Six-minute walk distance as a marker for disability and complaints in patients with systemic sclerosis. Clin Exp Rheumatol 2011; 29: 53-59.
26. Wells AU, Denton CP. Interstitial lung disease in connective tissue disease – mechanisms and management. Nat Rev Rheumatol 2014; 10: 728-739.
27. Du Bois RM, Nathan SD, Richeldi L, Schwarz MI, Noble PW. Idiopathic pulmonary fibrosis. Lung function is a clinically meaningful endpoint for phase III trials. Am J Respir Crit Care 2012; 186 (8): 712-715.
28. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-117.
29. Verschakelen JA, The role of high-resolution computed tomography in the work-up of interstitial lung disease. Curr Opin Pulm Med 2010; 16 (5): 503-510.

30. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology (Oxford) 2013; 52 (1): 155-160.
31. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Resp Crit Care Med 2008; 177 (11): 1248-1254.
32. Kocheril SV, Appleton BE, Somers EC, Kazerooni EA, Flaherty KR, Martinez FJ et al. Comparison of disease progression and mortality of connective tissue disease-related interstitial lung disease and idiopathic interstitial pneumonia. Arthritis Rheum 2005; 53: 549-557.
33. Walsh SLF, Sverzellati N, Devaraj A, Keir GJ, Wells AU, Hansell DM. Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants. Thorax 2014; 69: 216-222.
34. Winklehner A, Berger N, Maurer, Distler O, Alkadhi H, Frauenfelder T. Screening for interstitial lung disease in systemic sclerosis: the diagnostic accuracy of HRCT image series with high increment and reduced number of slices. Ann Rheum Dis 2012; 71 (4): 549-552.
35. Kowal-Bielecka O, Kowal K, Chyczewska E. Utility of bronchoalveolar lavage in evaluation of patients with connective tissue diseases. Clin Chest Med 2010; 31: 423-431.
36. Meyer KC. The role of bronchoalveolar lavage in interstitial lung disease. Clin Chest Med 2004; 25: 637-649.
37. Poletti V, Ravaglia C, Gurioli C, Piciucchi S, Dubini A, Cavazza A et al. Invasive diagnostic techniques in idiopathic interstitial pneumonias. Respirology 2016; 21 (1): 44-50.
38. Hagmeyer L, Theegarten D, Wohlschläger J, Treml M, Matthes S, Priegnitz C et al. The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease. Clin Respir J 2016; 10 (5): 589-595.
39. Raj R, Raparia K, Lynch DA, Brown KK. Surgical lung biopsy for interstitial lung diseases. Chest 2016. Epub ahead of print.
40. Molinari F, Eichinger M, Risse F, Plathow C, Puderbach M, Ley S et al. Navigator-triggered oxygen-enhanced MRI with simultaneous cardiac and respiratory synchronization for the assessment of interstitial lung disease. J Magn Reson Imaging 2007; 26: 1523-1529.
41. Ohno Y, Nishio M, Koyama H, Takenaka D, Takahashi M, Yoshikawa T et al. Pulmonary MR imaging with ultrashort TEs: Utility for disease severity assessment of connective tissue disease patients. Eur J Rad 2013; 82: 1359-1365.
42. Uehara T, Takeno M, Hama M, Yoshimi R, Suda A, Ihata A et al. Deep-inspiration breath hold 18F-FDG-PET/CT is useful for assessment of connective tissue disease interstitial pneumonia. Mod Rheumatol 2016; 26 (1): 121-127.
43. Owada T, Maezawa R, Kurasawa K, Okada H, Arai S, Fukuda T. Detection of inflammatory lesions by F-18 fluorodeoxyglucose positron emission tomography in patients with polymyositis and dermatomyositis. J Rheumatol 2012; 39: 1659-1665.
44. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease. A call for clarification. Chest 2010; 138 (2): 251-256.
45. Solomon JJ, Chartrand S, Fischer A. Current approach to connective tissue disease-associated interstitial lung disease. Cur Opin Pulm Med 2014; 20: 449-456.
46. Oldham JM, Adegunsoye A, Valenzi E, Lee C, Witt L, Chen L et al. Characterisation of patients with interstitial pneumonia with autoimmune features. Eur Resp J 2016; 47: 1767-1775.
47. Vij R, Noth I, Strek ME. Auto-immune-featured interstitial lung disease: a distinct entity. Chest 2011; 140 (5): 1292-1299.
48. Ferri C, Manfredi A, Sebastiani M, Colaci M, Giuggiolo D, Vacchi C et al. Interstitial pneumonia with autoimmune features and undifferentiated connective tissue disease: our interdisciplinary rheumatology-pneumology experience, and review of literature. Autoimmun Rev 2016; 15: 61-70.
49. Cottin V. Idiopathic interstitial pneumonias with connective tissue diseases features: A review. Respirology online 2015.
50. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 2015; 46 (4): 976-987.
51. Chartrand S, Fischer A. Management of connective tissue disease-associated interstitial lung disease. Rheum Dis Clin N Am 2015; 41: 279-294.
52. Silver KC, Silver RM. Management of systemic sclerosis-associated interstitial lung disease. Rheum Dis Clin N Am 2015; 41: 439-457.
53. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis: executive summary. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med 2015; 192 (2): 238-248.
54. Miura Y, Saito T, Fujita K, Tsunoda Y, Tanaka T, Takoi H et al. Clinical experience with pirfenidone in five patients with scleroderma-related interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31(3): 235-238.
55. Raghu G, Selman M. Nintedanib and pirfenidone. New antifibrotic treatments indicated for idiopathic pulmonary fibrosis offer hopes and raises questions. Am J Respir Crit Care Med 2015; 191 (3): 252-254.
56. Okuda R, Hagiwara E, Baba T, Kitamura H, Kato T, Ogura T. Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice. Resp Med 2013; 107: 1431-1437.
57. Wuyts WA, Kolb M, Stowasser S, Stansen W, Huggins JT, Raghu G. First data on efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis and forced vital capacity of ≤ 50% of predicted value. Lung 2016; 194 (5): 739-743.
58. Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS trials. Resp Med 2016; 113: 74-79.
59. Panopoulos ST, Sfikakis PP. Biological treatments and connective tissue disease associated interstitial lung disease. Curr Opin Pulm Med 2011; 17 (5): 362-367.
60. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (fascinate): a phase 2, randomized, controlled trial. The Lancet 2016; 387: 2630-2640.
61. Mori S. Management of rheumatoid arthritis patients with interstitial lung disease: safety of biological anti-rheumatic drugs and assessment of pulmonary fibrosis. Clin Med Insights Circ Respir Pulm Med 2015; 9: 41-49.
62. Keir GJ, Maher TM, Hansell DM, Denton CP, Ong VH, Singh S et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. Eur Respir J 2012; 40 (3): 641-648.
63. Keir GJ, Maher TM, Ming D Abdullah R, de Lauretis A, Wickremasinghe M et al. Rituximab in severe, treatment–refractory interstitial lung disease. Respirology 2014; 19: 353-359.
64. Rosenbloom J, Mendoza FA, Jimenez SA. Strategies for anti-fibrotic therapies. Biochem Biophys Acta 2013; 1832: 1088-1103.