Lung involvement in connective tissue diseases: A comprehensive review and a focus on rheumatoid arthritis

Benedetta Marigliano, Alessandra Soriano, Domenico Margiotta, Marta Vadacca, Antonella Afeltra *

Department of Clinical Medicine and Rheumatology, University Campus Bio-Medico of Rome, Italy

A B S T R A C T

The lungs are frequently involved in Connective Tissue Diseases (CTDs). Interstitial lung disease (ILD) is one of the most common pleuropulmonary manifestations that affects prognosis significantly. In practice, rheumatologists and other physicians tend to underestimate the impact of CTD-ILDs and diagnose respiratory impairment when it has reached an irreversible fibrotic stage. Early investigation, through clinical evidence, imaging and – in certain cases – lung biopsy, is therefore warranted in order to detect a possible ILD at a reversible initial inflammatory stage. In this review, we focus on lung injury during CTDs, with particular attention to ILDs, and examine their prevalence, clinical manifestations and histological patterns, as well as therapeutic approaches and known complications till date. Although several therapeutic agents have been approved, the best treatment is still not certain and additional trials are required, which demand more knowledge of pulmonary involvement in CTDs. Our central aim is therefore to document the impact that lung damage has on CTDs. We will mainly focus on Rheumatoid Arthritis (RA), which – unlike other rheumatic disorders – resembles Idiopathic Pulmonary Fibrosis (IPF) in numerous aspects.

© 2013 Elsevier B.V. All rights reserved.

Contents

1. Introduction ............................................................. 1077
2. Classification of interstitial lung diseases .......................... 1077
   2.1. The 2002 American Thoracic Society/European Respiratory Society Revised Classification .......................... 1077
   2.2. Connective tissue disorders versus idiopathic pulmonary fibrosis: are there any links? .......................... 1077
3. Histopathology ........................................................... 1078
   3.1. Idiopathic usual interstitial pneumonia vs. idiopathic non-specific interstitial pneumonia .......................... 1078
   3.2. Histological patterns in the lung in connective tissue disorders ............................................. 1078
   3.3. Organizing pneumonia: an exception ............................................. 1079
   3.4. Combined pulmonary fibrosis and emphysema ............................................. 1079
   3.5. Rheumatoid arthritis as a distinct entity ............................................. 1079
4. Rheumatoid arthritis and interstitial lung disease ..................... 1079
5. Therapy ............................................................... 1080
   5.1. CTD – interstitial lung disease – therapeutic approach ............................................. 1080
   5.2. Therapeutic developments in rheumatoid arthritis – interstitial lung disease .......................... 1080
   5.3. Lung transplantation ........................................................... 1081
   5.4. Drug toxicity ........................................................... 1081
6. Conclusions .................................................................. 1081
Disclosure statement .................................................................. 1081
Take-home messages .................................................................. 1081
References .................................................................. 1081

* Corresponding author at: Department of Clinical Medicine and Rheumatology, University “Campus Bio-Medico”, Via Alvaro de Portillo, 200, 00128 Rome, Italy. Tel.: +39 06 22 541 1209; fax: +39 06 22 541 456.
E-mail address: a.afeltra@unicampus.it (A. Afeltra).
1. Introduction

Lungs are often involved in connective tissue diseases (CTDs), with a noticeable effect on morbidity and mortality. The term “interstitial lung disease” (ILD) embraces a group of disorders characterized by inflammation and possibly pulmonary interstitial fibrosis, whose progression results in impaired oxygen transfer and scarring of the lung.

An ILD may be the first sign of a CTD and may precede extrapulmonary manifestations by years. ILDs may occur in all CTDs (overall incidence of 15%) and most often in Systemic Sclerosis (SSc), which justifies autoimmune screening in all patients with apparent idiopathic ILDs. A population-based study reported that 3.5% of patients with Rheumatoid Arthritis (RA) were diagnosed as having ILD prior to RA diagnosis [1]. Their prognosis and treatment varies depending upon the underlying CTD and radiological and histopathological patterns [2]. Around 25% of ILDs occur during “undifferentiated” CTDs (UCTDs), making it hard to distinguish them from an idiopathic interstitial alternative or a lung-dominant CTD [3].

A combination of patterns is frequently observed. Therefore finding abnormalities in more than one compartment upon imaging, histological or clinical analysis is a possible trait of an underlying CTD (Table 1). ILDs may be asymptomatic, but may be identified with high resolution computed tomography (HRCT) or pulmonary function tests (PFTs) [4] that are essential in determining the clinical significance of lung impairment [5]. However clear parameters for ILD staging have only been developed for SSc [3]. Very-low-radiation dose HRCT is much more sensitive in detecting changes in the parenchyma than chest X-rays [6], and can identify interstitial involvement in otherwise healthy asymptomatic patients, as reported by Winklehner et al. [7]. Detailed analysis has shown good correspondence between HRCT abnormalities and histological findings in ILD patients, as reported by Winklehner et al. [7].

2. Classification of interstitial lung diseases

2.1. The 2002 American Thoracic Society/European Respiratory Society Revised Classification

The American Thoracic Society/European Respiratory Society (ATS/ERS) revised the original classification in 2002 replacing the term ILD with diffuse parenchymal lung disease (DPLD), thus emphasizing that the parenchyma is the first site of damage and shifting the emphasis from histopathology to pathophysiology. These disorders are classified into four groups: 1) DPLDs of known association (drugs, CTDs, environmental and occupational exposure), 2) granulomatous DPLDs (such as sarcoidosis), 3) other and rare DPLDs (including: lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, pulmonary alveolar proteinosis, and eosinophilic pneumonia) and 4) idiopathic interstitial pneumonias (IPPs) [11].

IPPs include: non-specific interstitial pneumonia (NSIP) (split into cellular and fibrotic), usual interstitial pneumonia (UIP) (which includes its idiopathic counterpart: idiopathic pulmonary fibrosis (IPF)), diffuse alveolar damage (DAD), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis interstitial lung disease (RB-ILD) [12]. Diagnosis requires a combination of histopathological, clinical and radiological examinations [12]. For example, biopsies showing a NSIP fibrotic pattern in patients with radiographic and clinical features suggesting IPF (especially honeycomb lung) should be considered as IPF. Radiographic imaging is often sufficient for histopathological determination, while surgical lung biopsy is only required if radiographic imaging is not clear [13] (Table 2).

2.2. Connective tissue disorders versus idiopathic pulmonary fibrosis: are there any links?

IPFs are often mistaken for secondary ILDs. IPF is defined in the first group by its unremitting and deteriorating course. It is a chronic fibrosing interstitial pneumonia of unknown cause, which is restricted to the lungs and affects white smokers [14]. The characteristic histological pattern of IPF is UIP. The primary histological features of UIP/IPF include diffuse cellular inflammation, areas of proliferating myofibroblasts known as fibroblastic foci, and honeycombing [15]. Besides a UIP pattern, exclusion of known ILD causes, distinctive HRCT abnormalities, a restrictive ventilatory pattern and impaired gas exchanges are required to diagnose IPF. A probable IPF diagnosis can also be made without performing surgical lung biopsy if all the major criteria and three of the four minor criteria proposed by the ATS/ERS are met [16].

Significantly longer survival is seen in CTD-related diseases with a UIP pattern than in idiopathic ones. The incidence and prevalence of IPF are estimated at 10.7 cases per 100,000 per year and 20 cases per 100,000 respectively for males, and 7.4 cases per 100,000 and 13 cases per 100,000 respectively for females [17]. Prognosis in IPF is severe with a median survival of two to three years after diagnosis. Although the trend of IPF is an unremitting respiratory function decline, the course of individual patients varies noticeably: the majority undergoes a slow functional decline, the minority has a short disease with a fast progressive functional decline, and others suffer episodes of acute exacerbation with a collapse during the end stage of the disease. Acute exacerbation is defined as: 1) aggravation of dyspnoea in the space of a month, 2) hypoxemia with an arterial oxygen tension/inspired oxygen tension ratio of <225, 3) development of new pulmonary infiltrates in chest radiography, and 4) absence of apparent infection or heart disease [18].

The pathogenesis of IPF is still unknown. Unlike tumors, where there is a single point of origin, in IPF, multiple fibroblast foci appear in the lungs and new foci emerge as the disease progresses [19]. IPF does not seem to involve classical inflammatory pathways, as occurs in CTDs. Clinical experiments and official clinical trials show that a large variety of anti-inflammatory drugs have very little effect on the progression of this disease [20,21]. This does not mean that immune cells play no role in the progression of the disease, but rather suggest that general immunomodulation does not significantly change its course. IPF is considered an “epithelial–fibroblastic” disorder [22] where damaged

---

**Table 1** Pulmonary complications in CTDs.

<table>
<thead>
<tr>
<th>RA</th>
<th>SSc</th>
<th>SLE</th>
<th>PM/DM</th>
<th>SjS</th>
</tr>
</thead>
<tbody>
<tr>
<td>*** (UIP &gt; NSIP &gt; OP = DAD)</td>
<td>** (NSIP &gt; UIP)</td>
<td>* (NSIP &gt; DAD = LIP = OP = UIP)</td>
<td>*** (NSIP = OP &gt; DAD &gt; UIP)</td>
<td>**** (NSIP &gt; LIP &gt; OP = UIP = DAD)</td>
</tr>
<tr>
<td>* (Bronchiectasis and obliterative bronchiolitis)</td>
<td>* (Obliterative bronchiolitis)</td>
<td>*</td>
<td>* (Bronchiectasis)</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

* stands for infrequent; ***** stands for most frequent; abbreviations: UIP = usual interstitial pneumonia, NSIP = non-specific interstitial pneumonia, OP = organizing pneumonia, DAD = diffuse alveolar damage, LIP = lymphocytic interstitial pneumonia, PAH = pulmonary arterial hypertension.
alveolar epithelial cells modulate the initiation and development of a fibrotic environment, through numerous cytokines, such as endothelin-1 (ET-1), transforming growth factor beta (TGFbeta), and tumor necrosis factor alpha (TNFalpha) [23]. These cytokines are possible targets for therapy; one example is pirfenidone, a small antifibrotic agent that inhibits TNF-alpha and TGF-beta syntheses, which was approved for the treatment of mild to moderate IPF forms in Japan in October 2008 and in Europe in March 2011. The British Thoracic Society guidelines weakly recommend a triple therapy based on the outcome of the IFIGENIA trial [24]. It consists of prednisolone, azathioprine, and N-acetylcysteine. The more recent ATS/ERS guidelines, on the other hand, recommend lung transplantation or participation in a clinical trial [24–26] as treatment options. According to recently emerging data from the PANTHER study designed by the National Heart, Lung, Blood Institute, the IFIGENIA trial seems to be outdated since no benefit has been shown in IPF from steroids and azathioprine [27]. Participants receiving triple therapy experienced serious adverse events, had to discontinue drugs and showed an increased mortality risk [27]. Eleven percent of patients died in the triple therapy group, while 1% died in the placebo group. Approximately 50% of deaths resulted from respiratory disease, which has raised more questions than it has answered.

3. Histopathology

3.1. Idiopathic usual interstitial pneumonia vs. idiopathic non-specific interstitial pneumonia

Distinguishing UIP from NSIP has important prognostic implications: idiopathic UIP/IPF has a poor prognosis and lacks an appropriate treatment, whereas idiopathic NSIP has a good prognosis, with a five-year mortality rate of under 18% [28], and responds to anti-inflammatory treatment. The NSIP pattern affects middle-aged women, is more common in CTDs [29] and is found in several disorders, such as hypersensitivity pneumonitis [28]. The histopathology of fibrotic NSIP is characterized by uniformly distributed interstitial inflammation and/or fibrosis with a chronologically homogeneous fibrotic process, unlike UIP/UIP [30]. Fibroblastic foci and honeycombing are rare, whereas these foci are the main trait of UIP/UIP, which makes it hard to diagnose NSIP with radiology alone [31–34]. When HRCT and/or lung biopsy show probable NSIP, but there is insufficient data to suggest an alternative condition, it is more properly referred to as an “NSIP pattern”. The only HRCT feature independently associated with NSIP is ground glass attenuation. Therefore lung biopsy is often required for patients who may be good surgical candidates to confirm the certainty of the diagnosis. A NSIP pattern is encountered in patients with a distinct form of IIP: their clinical signs and disease course are highly specific, unlike those reported in patients with UIP/IPF. Diagnosis of idiopathic NSIP consequently requires multidisciplinary methods involving combined clinical, radiological and histological techniques [28]. Studies in idiopathic conditions have clearly shown that UIP/IPF is characterized by a worse survival rate than fibrotic NSIP [34,35].

3.2. Histological patterns in the lung in connective tissue disorders

A combination of histological patterns may be frequent in CTDs. The most frequent CTD-ILD histological patterns include: NSIP; UIP; OP seen in polymyositis (PM) and RA; UIP mainly found in Sjögren’s syndrome (SJS) and RA, associated with a good response to corticosteroids; and lastly, DAD seen in RA, PM, systemic lupus erythematosus (SLE) and UCTD. DAD can also infrequently occur on underlying fibrotic ILD as a life-threatening acute exacerbation or subacute presentation. Studies conducted after the 2002 ATS/ERS revision have shown that the most frequent pattern in CTD-ILD, excluding RA, is NSIP, unlike in IIPs, where the UIP pattern is found [36]. It is worth noting that patients previously diagnosed as affected with NSIP may very likely be found to have an underlying UCTD [29]. Since as many as 25% of patients with systemic autoimmune diseases do not meet the American College of Rheumatology (ACR) Classification criteria for definite CTD, it is extremely important to diagnose the distinct clinical entity of UCTD in ILD patients, also considering its better prognostic sequel compared with IPF [37,38]. Despite heterogeneity in terms of organ impairment, UCTDs involve lungs (often asymptomatic) in up to 67% of cases [39], with manifestations including: pleural effusions, pulmonary arterial hypertension (isolated or associated with an ILD), and ILDs with NSIP pattern [40,41]. ILD in UCTD has an effect on the prognosis and increases mortality rate: Gunnarsson et al. demonstrated a mortality rate of 3.3% after a four year follow-up in patients with normal HRCT compared with a 20.8% rate in patients with severe fibrosis [42].

Longer survival is seen in CTD-ILDs than in IPF, although no reason has yet been found for this. The better outcome in CTD-ILD might be related to the higher NSIP pattern frequency (with the exception of RA). In any case, if a UIP pattern is found in a CTD, survival is longer than in UIP/IPF [43]. Flaherty et al. reviewed 108 patients whose surgical lung biopsy showed a UIP pattern. They reported a lower abundance of fibroblastic foci and longer survival in CTD-UIP than in UIP/IPF [44]. A larger study also showed that CTD-UIP biopsies had fewer fibroblastic foci, a larger number of germinal centers with high inflammation scores and smaller honeycomb spaces than UIP/IPF biopsies [45]. This explains the better prognosis since a honeycombing score implies fibrosis. Germinal centers are instead sites of immunoglobulin (lg) class switching [46,47], where mutated lgG autoantibodies are generated. They are therefore sites of possible immune

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Histology</th>
<th>Radiology</th>
</tr>
</thead>
</table>
| NSIP    | - Uniform interstitial involvement  
- Rare honeycombing  
- Common honeycombing  
- Subpleural and peripheral fibrotic distributions  
- Masson bodies (plugs in airspaces)  
- Scarce interstitial impairment  
- Acute: edema and hyaline membranes  
- Chronic: airspace and interstitial distortion  
- Bronchiolocentric lymphoid tissue hyperplasia  
- Predominant distal airspace involvement with macrophage accumulation  
- Mild interstitial involvement  
- Bronchiolocentric macrophage accumulation and mild bronchiolar fibrosis | - Bilateral GGO, reticulation with bronchiectasis and bronchioleosis  
- Rare basal honeycombing  
- Scarce GGO, basilar reticulation  
- Honeycombing and traction bronchiectasis  
- Airspace consolidation with basal and peripheral distribution  
- Presence of air bronchograms  
- Acute: GGO and consolidation areas  
- Chronic: Traction bronchiectasis with reorganization  
- GGO with cysts  
- Occasional septal thickening and lung nodules  
- GGO with microcystic change and peripheral distribution  
- GGO with centrilobular nodules with upper and/or diffuse lung distribution |
| UIP     | - Temporal heterogeneity: scattered fibroblastic foci  
- Common honeycombing  
- Subpleural and peripheral fibrotic distributions  
- Masson bodies (plugs in airspaces)  
- Scarce interstitial impairment | |
| DAD     | - Acute: edema and hyaline membranes  
- Chronic: airspace and interstitial distortion | |
| LIP     | - Bronchiolocentric lymphoid tissue hyperplasia | |
| DIP     | - Predominant distal airspace involvement with macrophage accumulation  
- Mild interstitial involvement  
- Bronchiolocentric macrophage accumulation and mild bronchiolar fibrosis | |
| RB-ILD  | - Bronchiolocentric macrophage accumulation and mild bronchiolar fibrosis | |

Abbreviations: NSIP = non-specific interstitial pneumonia, UIP = usual interstitial pneumonia, OP = organizing pneumonia, DAD = diffuse alveolar damage, LIP = lymphocytic interstitial pneumonia, RB-ILD = respiratory bronchiolitis interstitial lung disease, GGO = ground glass opacities.
dysregulation [48], which is correlated with autoimmune mechanisms in CTD-UIP [45], and are the best discriminator between CTD and IPF. These histological findings may partially explain why the prognosis of patients with UIP in CTDs is better than those with UIP/IPF despite having the same disease pattern. Furthermore, no difference in survival was found between patients with idiopathic and CTD-NSIP patterns [49].

In conclusion, it is likely that the better prognosis in CTD-ILD does not only depend on the prevalence of a NSIP pattern, but is also influenced by the fact a CTD-UIP pattern is less “aggressive” than a UIP/IPF pattern [50].

3.3. Organizing pneumonia: an exception

Although the prognosis of CTD-ILD is generally better than that of IIPs, cryptogenic OP (COP), which belongs to the latter group, has a much better prognosis. Most patients with COP improve either after treatment or spontaneously [51,52]. OP appears in CTDs (including RA) with a more aggressive persistence and disease progression than its idiopathic counterpart [53–58]. In a study on 100 patients with OP diagnosed by lung biopsy (CTD 24 and COP 76), Jung-Wan Yoo et al. suggested that, although the overall prognosis was good with a low mortality rate associated with a high therapeutic response, recurrence and incomplete recovery were typical in the CTD-OP group [59].

3.4. Combined pulmonary fibrosis and emphysema

A retrospective study conducted by Cottin et al. identified a new syndrome among patients with CTDs, which they called combined pulmonary fibrosis and emphysema (CPFE) [60]. It is unclear whether CPFE is a distinct syndrome in susceptible individuals triggered by exposure to smoking or if it is just a particular member of the IPF family [61]. This syndrome is very important since parenchymal destruction increases the risk of pulmonary hypertension [62], and is directly responsible for the deaths among these patients [63,64]. Cottin et al. proposed introducing CPFE as a new lung disease category, since this syndrome was not only found in tobacco smoking environments. However cigarette smoking contributes enormously to the pathophysiology of the disease: the authors reported that all but four patients were current or past smokers [60]. Salient dissimilarities were found between “idiopathic” CPFE and CTD-CPFE, suggesting CTDs may play an etiological role. RA was by far the most common CTD with a CPFE pattern, when compared to other autoimmune disorders.

3.5. Rheumatoid arthritis as a distinct entity

Although the various CTDs associated with ILDs are often considered together because of their shared autoimmune nature, there are substantial differences in their clinical presentations and the way the CTD is managed in each specific CTD [65]. Evidence suggests that a UIP pattern in RA may be associated with shorter survival than in other CTDs: Park et al. described shorter survival in RA-UIP patients than in non-RA CTD UIP and NSIP individuals [50]. In a retrospective study conducted on eighteen RA-ILD patients, Hyun-Kyung Lee et al. showed that deaths occurred in the UIP group, while all the patients with NSIP were all either alive, improving or stable [36]. Furthermore, a study performed on 28 patients with RA-ILD found a notably greater trend towards shorter survival in UIP patterns than in NSIP: UIP patients often experienced acute recrudescence [50]. The authors of a 2008 review reported the likelihood of resistance to corticosteroid treatment in patients with RA-ILD and a UIP pattern, unlike those with RA-ILD and a NSIP or OP pattern [66]. When a UIP pattern is found in RA, it may be considered an independent prognostic factor. With the exception of RA, a difference in the fibrotic NSIP and UIP patterns on an underlying CTD does not allow prognostic separation. Surgical lung biopsy is therefore not necessary, also because HRT may be classified histologically. The main radiological signs of RA-ILDs include ground glass opacities, honeycombing, reticular patterns and consolidation [67] (Fig. 1).

4. Rheumatoid arthritis and interstitial lung disease

RA is the most frequent CTD, with a prevalence of 1–2% in the general population and female to male ratio of 3:1. Extra-articular manifestations are found in nearly 50% of RA patients [68], including splenomegaly, pericarditis, skin ulceration, subcutaneous nodules, increased rate of atherosclerotic artery disease and a multiplicity of pleuropulmonary manifestations [3]. Several studies [69–76] have reported impairment of one or more parts of the respiratory system, with a prevalence ranging from 4 to 68% [77]. The majority of lung diseases during the course of RA occur during the first five years after diagnosis. Airway injury seems to be the earliest manifestation [78] together with inflammatory airway diseases (IADs), including bronchiectasis and obliterative bronchitis, which is reported in more than 10% of cases [30]. When pulmonary hypertension is found, it is mild and often associated with ILDs, which are a more common manifestation that significantly affects the prognosis [12,79]. ILDs are the second cause of mortality (10% to 20%) [5] in RA after cardiac manifestations [80]. This may be partly explained by the predisposition to chest infections and the association with lung cancer, which is aided by smoking and immunosuppression [81,82]. Bongartz et al. reported a median survival for RA-ILD of 2.6 years compared to 9.9 years for RA alone [83]. Dawson et al. confirmed that a decrease in carbon monoxide transfer coefficient (DLCO) is also a sign of progression in lung fibrosis. They showed that a DLCO < 54% of the predicted value is highly specific for disease progression [84]. It is therefore recommended that all patients with CTDs are checked for ILDs.

RA-ILD affects twice as many men as women, especially those aged from 50 to 60 years. Prevalence also varies widely from 5 to 58% according to the ascertainment method, also considering that clinically significant forms of ILD affect no more than 50% of cases these days [85]. Many genetic, clinical, environmental and serological factors contribute to the development of RA-ILD. Genetic predisposition plays an important role [86]; several studies have reported more frequent polymorphisms at the HLAB40 and B54 antigen sites in RA-ILD [87,88], and these patients are less likely to be DR4 positive [89] and more likely to possess the site encoding for alpha1-protease inhibitor [90]. The majority of ILD involvement occurs in individuals with longstanding RA, especially male smokers. Smoking is a significant environmental risk factor,
with an odds ratio of 3.8 for ILD in RA patients with a smoking history >25 pack years [91]. Klaresegk et al. [92] put forward the idea that smoking generates a specific immune reaction to citrullinated proteins, thus playing a potentially pathogenic role in RA-ILD. Given this apparent combination of RA, smoking and anti-citrullinated protein antibody formation, one question that emerges is whether citrullination occurs in extra-articular tissues, such as the lung parenchyma. Finding anti-citrullinated peptide (anti-CCP) positivity usually suggests a greater risk of extra-articular complications in RA [8].

Studies have established the role of smoking in augmenting the expression of the lung citrullinating enzyme peptidylarginine deiminase 2 in the bronchial mucosa [93]. Several serological biomarkers can probably be used to predict the development of RA-ILD. High levels of serum IgM Rheumatoid Factor (RF) and anti-CCP seem to indicate progression of RA-ILD [94,95]. They are found in RA, both in scarcely symptomatic and completely asymptomatic individuals [96,97], and are the only warning of an underlying CTD in patients with a smoking history and/or ILD alone [98]. The pathogenic role of anti-CCP antibodies remains unclear. However, their presence in BAL fluids suggests that the lungs may be an antigenic source for anti-CCP antibody production [92]. This is supported by Fischer et al. [99], who also described a lone or associated ILD pattern resembling RA lung characteristics in patients with anti-CCP antibody positivity and lung disease without CTD.

5. Therapy

Every lung treatment strategy must include supportive care. Best supportive and palliative care approaches always play a central role and include:
- treatment of gastroesophageal reflux
- pulmonary rehabilitation
- low doses of opiates when dyspnoea is immovable
- oxygen therapy when mild to severe hypoxia occurs at rest and during exercise, and
- annual influenza and regular pneumococcal vaccination are recommended to reduce the risk of pulmonary infection.

5.1. CTD – interstitial lung disease – therapeutic approach

Although several studies have examined the impact of immunosuppressive therapy on secondary ILDs, additional research is required to determine the optimal treatment strategies for each distinct form of CTD-ILD [65]. In the absence of randomized controlled trials, treatment of RA-ILD is essentially empirical and follows the same principles applied to any CTD (with the exception of SSc-ILD).

The rate of disease progression and the extent of lung injury are the two main factors considered when deciding whether a patient with CTD-ILD may benefit from immunosuppressive therapy. Markers of the likelihood of ILD progression include: short duration of systemic disease, underlying CTD, disease activity, recent functional decline, likelihood of response based on radiographic and histopathological patterns, age of patient, and ability to comply with treatment and monitoring [68]. Response is seen as an improvement or stabilization according to the preponderance of inflammation or fibrosis. Stabilization of lung function is defined when vital capacity (VC) and/or gas transfer remain within a 5% range over a two year period while improvement is defined by a 10% increase in either measurements corroborated by HRCT findings [100]. It is important to follow up with at least one PFT a year and HRCT scanning every other year, to reduce radiation exposure (less often in limited diseases).

Extent of lung damage is used to guide the therapeutic approach. Twenty percent lung impairment was the cut off value originally adopted by Goh et al. for SSc to distinguish a limited disease from an extensive disease, and this value has recently been found to apply to RA-ILD by Dawson et al. A limited disease generally requires conservative management: observation and deciding step by step if treatment is crucial. If needed, initial treatment consists of oral prednisone (0.5–1 mg/kg) and azathioprine (2–3 mg/kg), gradually tapered to maintenance levels when response occurs.

In a widespread ILD, management options include corticosteroids, starting with a dose of 0.5–1 mg/kg in all CTDs except SSc (because of the risk of renal crisis), possibly associated with an oral immunosuppressant. Azathioprine is most commonly used (starting with a 50 mg dose once a day for a month; if well tolerated the dose is increased to 150 mg a day) although mycophenolate (starting with 250 mg twice a day with 500 mg increases at 2 to 4 weekly intervals until full dose is reached: 1 g twice daily) may be better tolerated. If there is a response, prednisone is gradually reduced to a stable dose of 10 mg once a day in 6–12 months [3].

Pulsed intravenous methylprednisolone (7–10 mg/kg) and intravenous cyclophosphamide (10–15 mg/kg) at three week intervals for six months have a recognized place in the treatment of aggressive CTD-ILDs, such as an OP/DAD overlap. If a successful outcome is achieved with functional stability after six months, substitution of the intravenous cyclophosphamide with an oral immunosuppressant (azathioprine 1–2 mg/kg) at a constant dose for the next two to three years is recommended [101,102]. Immunosuppressive treatment should always be reduced gradually. Although these agents have been reported to stabilize or improve respiratory status, their routine use cannot be recommended without stronger evidence [65]. If there is no response or if life-threatening situations appear, despite adequate immunosuppression, a rescue therapy with rituximab is suggested, although its use is not supported by recognized studies. The experimental scheme is as follows: 1 g followed, after two weeks, with an additional gram [3]. If the disease progresses towards a functional decline, despite maximal immunosuppression, lung transplantation should be considered.

5.2. Therapeutic developments in rheumatoid arthritis – interstitial lung disease

The first line therapy for patients with newly diagnosed RA-ILD is high dose prednisone [103]. There is no strong evidence for additional immuno-suppressive therapies. Newer agents have been cited including mycophenolate mofetil [24], rituximab, imatinib and tocilizumab [104].

Mycophenolate has been shown to stabilize RA-ILD at doses of 1–2 mg a day in patients with limited diseases, although it does not always appear to be effective in ameliorating the articular manifestations of the disease (which require the coprescription of a disease modifying anti-rheumatic drug (DMARD)) [100]. This again illustrates that specific pulmonary disease monitoring is fundamental because the course of the ILD does not always follow the systemic disease.

Rituximab is a monoclonal antibody against the B-cell marker CD20, developed for B cell lymphomas, that has been licensed for the treatment of RA in anti-TNF non-responders. Several reports have shown promising results in the lung diseases that complicate SLE and other autoimmune disorders: one patient with UC/T2DM improved after just two doses, while a woman with polymyositis returned to near normal function after four treatments [105]. The safety and efficacy of Rituximab are currently under investigation for patients with RA-ILD.

Imatinib is a tyrosine-kinase inhibitor used in the treatment of chronic myeloid leukemia that has also been suggested in the treatment of SSc and RA [106]. A recent report put forward possible efficacy when combined with cyclophosphamide in the treatment of ILD [107].

Tocilizumab is a humanized antimouse IL-6 receptor monoclonal antibody. It may potentially modify the process of ILD and other systemic manifestations of RA since IL6 is expressed in a large proportion of cells in rheumatoid synovial tissue [108] and its increase has been shown to correlate with various indices of disease activity [109,110].

Given the therapies commonly used to treat RA, drug induced pneumonitis has to be considered in the differential diagnosis of RA-ILD. In
spite of limited data, cyclophosphamide (10–15 mg/kg) is usually administered intravenously in combination with methylprednisolone (7–10 mg/kg) at three-week intervals for six courses in RA-ILD patients with extensive or rapidly progressing lung disease [100]. At the end of this treatment, it is important to reassess lung function. Responders are widely treated with low-dose oral prednisone and azathioprine (1–2 mg/kg) to maintain response, often on an indefinite basis [100].

5.3. Lung transplantation

Pulmonary fibrosis is the second most frequent disease treated with lung transplantation, and it has the best outcome if compared with other pulmonary conditions requiring this operation [111,112]. Lung transplant is suggested when the disease is at its end stage: widespread (DLCO <40%) and/or progressive (>10% decline in FVC and or >15% decline in DLCO) [25]. For many individuals and for IPF patients in particular, lung transplant is the final option that offers a possible survival benefit. Considering the progressive unremitting course of IPF, these patients have a dismal prognosis on the transplantation waiting list [113,114]. The 6MWD may be used to assess the suitability of candidates eligible for transplantation. The distance they walk may be considered a valid prognostic indicator: for example, a walking distance of less than 207 m is associated with a four-fold increase in mortality [115]. Single lung transplantation should be considered jointly by a pulmonologist and rheumatologist for younger patients (under the age of 60 years) with advanced disease and no other significant comorbidity, when their articular disease is not the limiting factor in terms of exercise tolerance. Although end-stage transplantation is the best option, only 40% of patients live for more than five years after the operation [116]. This is probably due to transplantation-associated complications. One important example is bronchiolitis obliterans syndrome (BOS), a chronic lung allograft rejection with a complex pathophysiology characterized by intraluminal airway fibrosis, which limits long-term survival [117]. The lipid mediator leukotriene B4 has been found to be upregulated in patients with BOS during its convoluted pathogenesis. This mediator exerts a chemotactic activity on T lymphocytes through BLT1, a receptor expressed on T lymphocytes, which underlines its key pathogenic role [118]. In a pilot study on eleven patients with BOS, the addition of montelukast (a leukotriene inhibitor used in asthma) to the immunosuppressive therapy decreased the decline in FEV1 over a six month period [119]. This not only demonstrates the centrality of the leukotriene pathway, but also suggests that montelukast may play a therapeutic role in the long-term survival of transplanted patients [120].

5.4. Drug toxicity

Several DMARDs may cause lung reactions identical to those related to RA, thus delaying diagnosis and worsening prognosis. In general, immunosuppressive agents may cause infectious and non-infectious manifestations including: vasculitis, hypersensitivity pneumonitis, ILDs and sarcoid-like diseases [121]. ILDs and sarcoid-like diseases are frequent adverse manifestations. The latter are reversible, whereas ILDs are often associated with a dismal outcome [122]. Therefore, a thorough review of the medications used is essential in order to diagnose drug-induced pneumonitis (with the exclusion of concurrent infections) in the differential diagnosis of patients with suspected RA-ILD [65].

The ACR recommends avoiding methotrexate in patients with RA-ILD [123]. Some rheumatologists recommend that patients with RA who are about to start methotrexate treatment undergo a baseline chest X-ray and PFTs. These can be used as baseline measurements if respiratory symptoms develop [124], although no formal guidelines have been developed. Methotrexate lung reactions occur with a frequency ranging from 0.3 to 11.6% during the first year of treatment [125]. Methotrexate-ILD usually starts with subacute clinical symptoms (fever, cough and dyspnoea), BAL eosinophilia and lymphocytosis. HRCT shows honeycombing and subpleural nodules [51] and histology reveals granulomas and interstitial pneumonitis [3]. Other histological patterns observed in methotrexate-ILD include NSIP and OP. The ALI/DAD pattern is usually detected in acute life-threatening manifestations. Drug cessation and corticosteroid treatment are responded to well.

Leflunomide and gold salts have been associated with a lung reaction with an ALI/DAD pattern and significant impact on mortality in 1% of cases, while sulfasalazine and related compounds have been associated with OP and NSIP patterns. Drug-induced pneumonitis seems to have a genetic link: leflunomide-induced pneumonitis appears to occur more frequently in Japanese patients [126].

The role of biological therapies remains controversial to date [127]. Evidence shows that a pre-existing ILD is a risk factor in general and has a harmful effect on patients receiving anti-TNF agents in particular [128]. These agents have been linked with non-infectious granulomatous lung disease [129–131], lymphoistiophilic infiltration, new rheumatoid nodules, cases of fatal acute lung injury (ALI) (one after only three doses of infliximab) [132] and a case of fatal ILD exacerbation (after receiving etanercept) [133]. Drug-induced lung toxicity was proved by the British Society for Rheumatology Biologics Register (BSRBR), which prospectively collected data concerning patients with RA treated with biological therapies in the UK, and by Dixon et al., who demonstrated a higher prevalence of interstitial pneumonia (2.9% vs. 1.8% P = 0.002) [134] with UIP and NSIP patterns among 9294 RA patients treated with anti-TNF agents [135].

Rituximab may rarely complicate ILDs: two cases of fatal progressive ILD have been reported in patients receiving rituximab together with multi-agent chemotherapy [136].

6. Conclusions

All new RA patients should be assessed by establishing their basic respiratory history (smoking, cough and dyspnoea) and by examination (nail clubbing and basal crackles). Those with possible ILD and patients commencing methotrexate and anti-TNF biologic agent have to perform a chest X-ray and undergo PFTs (spirometry and DLCO). According to the British Society for Rheumatology guidelines, HRCT is required if abnormalities are found in order to determine whether the extent of lung involvement is extensive (>20%) or limited (<20%). When the assessment scan is borderline, PFTs are decisive: if VC is less than 70% of the predicted value, the patient’s disease is extensive. This approach has been shown to correlate with prognosis over long periods of time and its validity in RA-ILD has been reported by Dawson et al. [137]. However, if it is decided to treat RA-ILD, the current first line therapy is prednisone, and there is little evidence in the use of additional immunosuppressive therapies. In conclusion, collecting a full medication history is fundamental. It is also essential to perform further controlled therapeutic trials in order to find a less toxic treatment with long term efficacy.

Disclosure statement

The authors declare no conflicts of interest.

Take-home messages

- ILDs complicate the natural course of CTDs and have a negative prognostic value.
- RA-ILD has a more aggressive behavior than other CTD-ILDs, which resembles IPF.
- It is important to detect ILDs during CTDs promptly in order to start treatment early.
References


[126] Hagiwara K, Sato T, Takagi-Kobayashi S, Hasegawa S, Shigihara N, Akiyama O. Idiopathic inflammatory myopathies are a heterogeneous group of chronic muscle diseases of unknown etiology, primarily characterized by skeletal muscle immunoinflammatory damage and dysfunction. Serum autoantibodies, clonally-expanded T cell infiltration and HLA Class I antigen overexpression are characteristic essential findings in muscle tissues, strongly supporting an autoimmune pathogenesis. Muscle cells are the main target of the autoimmune response, and both adaptive and innate immunity take part in inducing and maintaining muscle fiber damage. Muscle cell degeneration and regeneration are characteristic features of inflammatory myositis. Recently, evidence is increasing about the crucial role of regenerating immature muscle cells in both the induction and perpetuation of muscle autoaggression, as discussed in the review article by Tournadre and Miossec (Nat Rev Rheumatol 2013; doi:10.1038/nrrheum.2013.26). The adaptive immune system is mainly represented by T helper type 1 and type 17 cells in muscle patients with autoimmune myositis. IL-1 and TNF proinflammatory cytokines are overexpressed by mononuclear and endothelial cells, and both induce IL-6 production by activated muscle cells. The innate immune response is involved as well, as suggested by the type I INF signature upregulation and association with disease activity and progression. Together with plasmacytoid dendritic cells, also immature muscle precursors are local producers of type I INF in inflamed muscle. Furthermore, it has been recently demonstrated that regenerating muscle precursors, differently from mature muscle fibers, characteristically overexpress HLA Class I antigens, myositis autoantigens, TLR3 and TLR7, thus being primarily involved in the induction of both innate and adaptive immune responses in injured muscle tissue. In conclusion, regenerating immature muscle cells might act as immunologically effective elements in susceptible individuals, by promoting and self-sustaining local autoimmune aggression towards themselves, thereby compromising muscle tissue repair.

Anna Ghirardello, PhD

Regenerating immature muscle cells have a key role in the pathogenesis of inflammatory myopathies

Idiopathic inflammatory myopathies are a heterogeneous group of chronic muscle diseases of unknown etiology, primarily characterized by skeletal muscle immunoinflammatory damage and dysfunction. Serum autoantibodies, clonally-expanded T cell infiltration and HLA Class I antigen overexpression are characteristic essential findings in muscle tissues, strongly supporting an autoimmune pathogenesis. Muscle cells are the main target of the autoimmune response, and both adaptive and innate immunity take part in inducing and maintaining muscle fiber damage. Muscle cell degeneration and regeneration are characteristic features of inflammatory myositis. Recently, evidence is increasing about the crucial role of regenerating immature muscle cells in both the induction and perpetuation of muscle autoaggression, as discussed in the review article by Tournadre and Miossec (Nat Rev Rheumatol 2013; doi:10.1038/nrrheum.2013.26). The adaptive immune system is mainly represented by T helper type 1 and type 17 cells in muscle patients with autoimmune myositis. IL-1 and TNF proinflammatory cytokines are overexpressed by mononuclear and endothelial cells, and both induce IL-6 production by activated muscle cells. The innate immune response is involved as well, as suggested by the type I INF signature upregulation and association with disease activity and progression. Together with plasmacytoid dendritic cells, also immature muscle precursors are local producers of type I INF in inflamed muscle. Furthermore, it has been recently demonstrated that regenerating muscle precursors, differently from mature muscle fibers, characteristically overexpress HLA Class I antigens, myositis autoantigens, TLR3 and TLR7, thus being primarily involved in the induction of both innate and adaptive immune responses in injured muscle tissue. In conclusion, regenerating immature muscle cells might act as immunologically effective elements in susceptible individuals, by promoting and self-sustaining local autoimmune aggression towards themselves, thereby compromising muscle tissue repair.