Curr Pulmonol Rep (2015) 4:135–141
DOI 10.1007/s13665-015-0121-9

INTERSTITIAL LUNG DISEASE (E ALHAMED, SECTION EDITOR)

Rheumatoid arthritis-associated interstitial lung disease

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Published online: 10 July 2015

Abstract Rheumatoid-associated interstitial lung disease (RA-ILD) is an important extra-articular manifestation of rheumatoid arthritis (RA), contributing to significant morbidity and mortality. Mortality is increased by 3-folds in RA-ILD patients in contrast with those without ILD. RA-ILD is frequently observed in males, and the risk of developing ILD is associated with older age at time of RA onset, male gender, and greater RA disease severity. Usual interstitial pneumonia (UIP) being the most common, with the worst prognosis. RA-ILD patients with UIP pattern tend to be older, more likely to be males, and have a more significant smoking history and worse survival. In contrast, those without the UIP pattern tend to be younger, more likely to be women, and have a less significant smoking history. This review discusses the diagnosis and therapeutic option in the management of RA-ILD.

Keywords Rheumatoid arthritis · Interstitial lung disease · Subtypes · Humans · Diagnosis · Treatment

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology. It is characterized by symmetrical arthritis and synovial inflammation leading to progressive joint erosions and eventually deformity if not treated [1••]. It affects approximately 0.5–1 % of the European and North American adults [2]. The etiology of RA is unknown; however, initiation of disease seems to result from an interaction among genetic susceptibility, clinical, serological, and environmental triggers. In addition to articular disease, patients develop extra-articular manifestations (EAM) with a 10-year cumulative incidence of more than 50 % involving the heart and vascular system, lungs, skin, and eyes contributing to the additional morbidity and mortality of patients with RA [3]. Pulmonary involvement is common and manifests as pleural disease, airway disease such as bronchiolitis obliterans, rheumatoid nodules, and in particular, interstitial lung diseases (ILD). ILD is the most important pulmonary manifestation of RA, contributes to considerable morbidity, and a commonest pulmonary cause of death in these patients [4]. However, rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is not a single type of ILD, but rather is composed of a spectrum of histological types with different associated patterns of clinical presentation, radiographic features, response to treatment, and clinical course.

This article is part of the Topical Collection on *Interstitial Lung Disease*

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Rheumatoid associated interstitial lung disease

Epidemiology pulmonary involvement in RA was first described by Ellman and Ball [5], who in 1948 reported three cases in which the typical presentation of RA and extensive pulmonary disease appeared to be associated with the same underlying process. In two cases, autopsy of the lungs showed a chronic fibrosing type of pneumonitis. Since its first description, it has become clear that RA-ILD includes a broad spectrum of disorders that differ greatly in their clinical presentation, pathology, and prognosis [6•, 7••]. Several studies have provided the prevalence of ILD among patients with RA widely variable; ranging between 3.6 and 61 % [1••, 8••]. This can

be attributed to inconsistency of clinical criteria used to define the condition, methods used for disease detection, and heterogeneity of study populations. Identification of ILD is further perplexed by the fact that many of the drugs used for the treatment of RA have potential harmful effects on the lungs. Sihvonen et al reported an autopsy study of 81 patients with longstanding RA that showed that 16 % died of respiratory failure, while 34 % had ILD [9]. The lifetime risk of developing ILD is substantially higher in RA patients than in those without RA, as illustrated by a population-based study by Bongartz et al [10]. In his cohort of 582, RA patients were followed for a mean of 16.4 years and compared with a matched cohort of 603 controls. The cumulative 30-year risk of ILD in these respective groups was 7.7 and 0.9 %, which translated into a hazard ratio of 8.96 (95 % CI, 4.02–19.94). Kinoshita et al reported RA-ILD organizing pneumonia (OP) preceding joint symptoms of RA within the average of first 12 months of diagnosis of OP [11]. Although RA is predominant in females, RA-ILD is frequently observed in males with a 2:1 male to female ratio [12••]. The risk of developing ILD was associated with older age at the time of RA onset, male gender, and greater RA disease severity [13]. Moreover, RA patients who developed ILD had a 3-fold increase in mortality in contrast with RA patients without ILD [3]. The poor prognosis of RA-ILD highlights the need for clinicians to be acquainted with the clinical presentation of this condition and be cognizant of its course and management.

Risk factors

Several environmental, serological, clinical, and genetic factors have been associated with the occurrence of RA-ILD. Smoking represents an independent risk factor in the development of ILD increasing the risk by 2.21-folds and approximately 3.8-fold increase of risk for ILD among patients with a smoking history of ≥25 packs-years [8•]. Occupational exposure, such as silica inhalation, contributes to the development of chronic lung inflammation-related ILD [1••]. Demographic factors age ≥65 years, male sex, and low social economic status are associated with increased susceptibility for the development of RA-ILD [14, 15]. Genetic polymorphisms studied in RA-ILD have shown certain polymorphisms of the human leucocyte antigen (HLA)-DRB shared epitope to be associated with increased risk of ILD (e.g., HLA-DRB1*1502 and *1502) [16]. Sugiyama et al reported an increased frequency of HLA-B54 and HLA-DR4 polymorphisms in patients with RA-ILD [17, 18]. Severity of RA in presence of erosive joint disease, high levels of erythrocyte sedimentation rate (ESR), and presence of rheumatoid nodules are risk factors for the development of RA-ILD [10, 13, 15]. Mori et al have shown high titers of rheumatoid factor (>100 IU/ml) significantly increased risk of RA-ILD as well as the presence of anti-cyclic citrulinated peptide antibodies (anti-ACPA) [7••, 10, 16].

Histopathology subtypes of RA-ILD

The consensus classification for idiopathic interstitial pneumonias (IIPs) proposed by the American Thoracic Society and the European Respiratory Society (ATS/ERS) [19] has been adopted to define RA-ILD [20, 21]. Table 1 summarizes the different histological and radiological patterns of RA-ILD. Several histopathological subtypes of ILD can be observed in RA patients. RA-ILD can present as any of the seven idiopathic interstitial pneumonias accordingly to the ATS/ERS consensus classification. The most frequent histopathological pattern of RA-ILD is usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP); other forms including lymphocytic interstitial pneumonia (LIP) and organizing pneumonia (OP) have been less commonly observed [20, 21]. In some patients, a combination of histopathologic types may be present, in which case a determination of the dominant type is made. RA-ILD patients with UIP pattern tend to be older, more likely to be males, and have a more significant smoking history and worse survival [7••]. In contrast, those without the UIP pattern tend to be younger, more likely to be women, and have a less significant smoking history [22••, 23]. Tsuchiya et al reported that patients with the DAD histopathological pattern of RA-ILD had the highest mortality, with a median survival time of 0.2 years [21].

RA-ILD diagnosis

The clinical symptoms of RA-ILD are nonspecific and some patients may be asymptomatic with proven RA-ILD. Majority of the patients' symptoms reported are with exertional dyspnea, dry cough, wheezing, pleuritic chest pain, fever, haemoptysis, and tachypnea [24]. Basal cripitations are the most frequent finding on chest examination [20, 24, 25].

Plain chest radiography demonstrates reticular and fine nodular opacities, commonly concentrated in the lower lung zones. Early in the disease, these changes may appear as patchy, alveolar-filling infiltrates, and as the disease progresses it is a more reticulonodular pattern [12••]. Rarely, lymphadenopathy, rheumatoid nodules, and pleural effusions may be present [19]. Chest radiography can be normal in early stages and is of low sensitivity for detection of ILD [12••, 25].

Pulmonary function test (PFT) demonstrates a restrictive defect with low forced vital capacity (FVC), low total lung capacity (TLC) with or without low diffusion capacity of the lung for carbon monoxide (DLCO), and hypoxemia at rest or on exertion [20]. Decreased DLCO has been described in up to 40 % of RA patients with or without signs and symptoms of

Table 1 Histological and radiological patterns of RA-ILD [1••]

Pattern	Histology	CT features	CT differential diagnosis
UIP	Subpleural and peripheral fibrosis. Fibroblastic foci, lymphoid aggregates With germinal centers and honeycombing are characteristic. Mild inflammation; architectural destruction.	Peripheral, subpleural, basal reticulation, and honeycombing Traction bronchiectasis, architectural distortion, GGO (less diffuse). Subpleural lines	IPF, other collagen vascular diseases, hypersensitivity pneumonitis (micronodules and sparing of lung bases), sarcodosis, asbestosis (pleura thickening).
NSIP	Uniform interstitial involvement; various degrees of fibrosis and/or inflammation. Lymphoid aggregates. Rare honeycombing	Bilateral, symmetrical, patchy, mainly basal GGO, possible reticulation, traction, bronchiectasis, irregular lines, or consolidation. Little or no honeycombing (in fibrosing NSIP).	UIP. DIP, COP, hypersensitivity pneumonitis, and HIV-associated interstitial lung disease.
OP	Connective tissue plugs within small airways and air spaces (Masson bodies). Little or no inflammation or fibrosis.	Patchy and multiple airspace consolidation, mainly basal, peripheral, or peribronchovascular. Air bronchograms can be seen. Possible associated GGO or centribular nodules.	Infections, vasculitis, sarcoidosis, alveolar carcinoma, lymphoma, eosinophilic pneumonia, NSIP, and COP.
DAD	(i) Acute phase: hyaline membranes, edema. (ii) Organizing phase: airspace and interstitial organization	(i) Acute phase: progressive, patchy, or diffuse GGO and dependent consolidation, often with lobular sparing (ii) Organizing phase: reticulation, traction bronchiectasis, and architectural distortion.	Hydrostatic edema, pneumonia, eosinophilic pneumonia, and ARDS (but more symmetrical and lower lung zones)
DIP	Extensive macrophage accumulation in the distal air spaces. Mild interstitial involvement	Patchy GGO, basal, and peripheral. Microcystic changes within GGO, reticular lines	RB-ILD, hypersensitivity pneumonitis, sarcoidosis, and *Pnuemocystis jiroveci* pneumonia.
RB-ILD	Bronchiolocentric macrophage accumulation. Mild bronchiolar fibrosis	Diffuse/upper lobes distribution, centrilobular nodules, bronchial wall thickening, and patchy GGO.	DIP, NSIP, and hypersensitivity pneumonitis
LIP	Bronchiolocentric lymphoid tissue hyperplasia	Diffuse, GGO, centrilobular nodules, septal thin-walled r nodules, septal thin-walled cysts, and lymph node enlargement	Sarcoidosis, lympangitic carcinoma, and Langerhans' cell histiocytosis

GGO ground glass opacities, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *COP* cryptogenic organizing pneumonia, *DAD* diffuse alveolar damage, *DIP* desquamative interstitial pneumonia, *RB-ILD* respiratory bronchiolitis-associated interstitial lung disease, *LIP* lymphoid interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis

pulmonary disease [25]. In the situation where the developing lung disease has caused a fall in gas transfer of 5 % from the previous normal level for that patient and/or impaired gas exchange characterized by an increase P (A-a) O2 (alveolar-arterial pressure difference for O2), decreased PaO2 at rest or exertion [26], this may be that ILD is not yet detectable on the high resolution computed tomography (HRCT) scan although the TLCO is below the normal range. This would be consistent with reports by Dawson et al of milder forms of idiopathic pulmonary fibrosis that are not evident on HRCT scans but have been found in lung biopsy specimens [25]. The most sensitive test appeared to be measurement of residual volume (RV). A reduction of >1 SD below the predicted RV was 83 % specific for ILD [25].

HRCT has been accepted as a standard noninvasive method of diagnosing and following RA-ILD. The results of HRCT have been shown to correspond closely with those of open lung biopsy. The ATS/ERS, in collaboration with the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT), published HRCT criteria for the diagnosis of UIP. The main criteria for UIP in HRCT (all four features must be present) are the following: subpleural, basal predominance; reticular abnormality; honeycombing with or without traction bronchoectasis; and absence of features listed as inconsistent with the UIP pattern. Inconsistent with the UIP pattern are any of the following seven features: upper or mid-lung predominance; peribronchovascular predominance; extensive ground-glass abnormality (extent>reticular abnormality; profuse micronodules (bilateral, predominately upper lobes); discrete cysts (multiple, bilateral, at a distance from areas of honeycombing; diffuse mosaic attenuation/air trapping (bilateral, in three or more lobes); and consolidation in bronchopulmonary segments [19].

Assayag et al reported in a cohort of 69 patients with RA-ILD to have a UIP pattern on HRCT to have 96 % specificity, with histological findings and a possible predictive value of 95 % [27••]. Raghu et al prospectively assessed the correlation between clinical, radiologic, and pathologic diagnosis of ILD in patients referred to a tertiary care center. Among 29 patients with a histopathologic diagnosis of idiopathic pulmonary fibrosis (IPF), HRCT had a specificity of 90 % and a sensitivity of 79 % [28]. In a retrospective study by Kim et al investigating specific HRCT features in patients with RA-ILD, it was found that reticulation, traction bronchoectasis, and honeycombing were significantly associated with worse survival time [23]. The findings of this study suggest that histopathologic UIP in RA-ILD can be determined with a high degree of confidence with the radiologic UIP pattern present on a HRCT. Given emerging data that identifying histopathologic UIP has important clinical implications for RA-ILD patients, this method of identifying it without the risk and cost of surgical lung biopsy is valuable. Because reliability and a high positive predictive value are critical for a surrogate diagnostic test for histopathology UIP, it is proposed that only radiologic UIP pattern be considered diagnostic of histopathology UIP in RA-ILD.

Bronchoalveolar lavage (BAL) is not routinely used as a diagnostic modality in RA-ILD because BAL changes may be seen even in the absence of ILD. BAL characteristics in RA-ILD patients show a predominance of neutrophils and macrophages [29]. The analysis of BAL fluid may not be helpful to distinguish between different subtypes of RA-ILD; however, a slightly higher percentage of neutrophils (4 %) may be more frequent in UIP. BAL may also be useful in excluding infectious processes, eosinophilic pneumonia, alveolar hemorrhage, or malignancy.

Surgical lung biopsy is the only definitive procedure to accurately diagnose an interstitial lung disease, but this is rarely required in RA-ILD as suggested by the joint ATS/ERS statement [26]. Additionally, there may be a 20 % increase in mortality if an open lung biopsy is performed in the setting of an acute exacerbation of ILD. If surgical lung biopsy is required for diagnostic uncertainty, video-assisted thoracoscopic surgery (VATS) is done which is a very safe and well tolerated procedure [30].

The usefulness of transthoracic ultrasound in the evaluation of lung diseases has been highlighted in the past decades. Maezadi et al have shown transthoracic ultrasound of the lung might be a sensitive noninvasive and radiation-free tool to observe early stage interstitial lung disease in rheumatic diseases [31•, 32•].

Figure 1 describes a diagnosis strategy for patients suspected to have RA-ILD. This is based on the findings of clinical features and/or presence of risk factors for ILD in patients with RA.

RA-ILD treatment

There are no randomized placebo-controlled therapeutic trials performed to date in RA-ILD. As such, no consensus therapeutic guidelines have been established. There is evidence that synthetic disease-modifying antirheumatic drugs (DMARDs) and biological DMARDs have shown to induce or exacerbate pre-existing RA-ILD. A recent meta-analysis has shown that methotrexate (MTX), leflunomide (LEF), tumor necrosis factor inhibitors (TNFi), rituximab (RTX), and tocilizumab (TCZ) may induce pneumonitis or worsen RA-related pre-existing ILD [33••]. The decision to start treatment is not always easy as RA-ILD may remain stable for years, and aggressive therapy may cause severe life-threatening side effects. Patients need to be closely monitored for progression of disease, and treatment is initiated when clinical symptoms manifest or when there is physiologic evidence of progressive disease. In all cases, risk of therapy must be weighed against threat of disease.

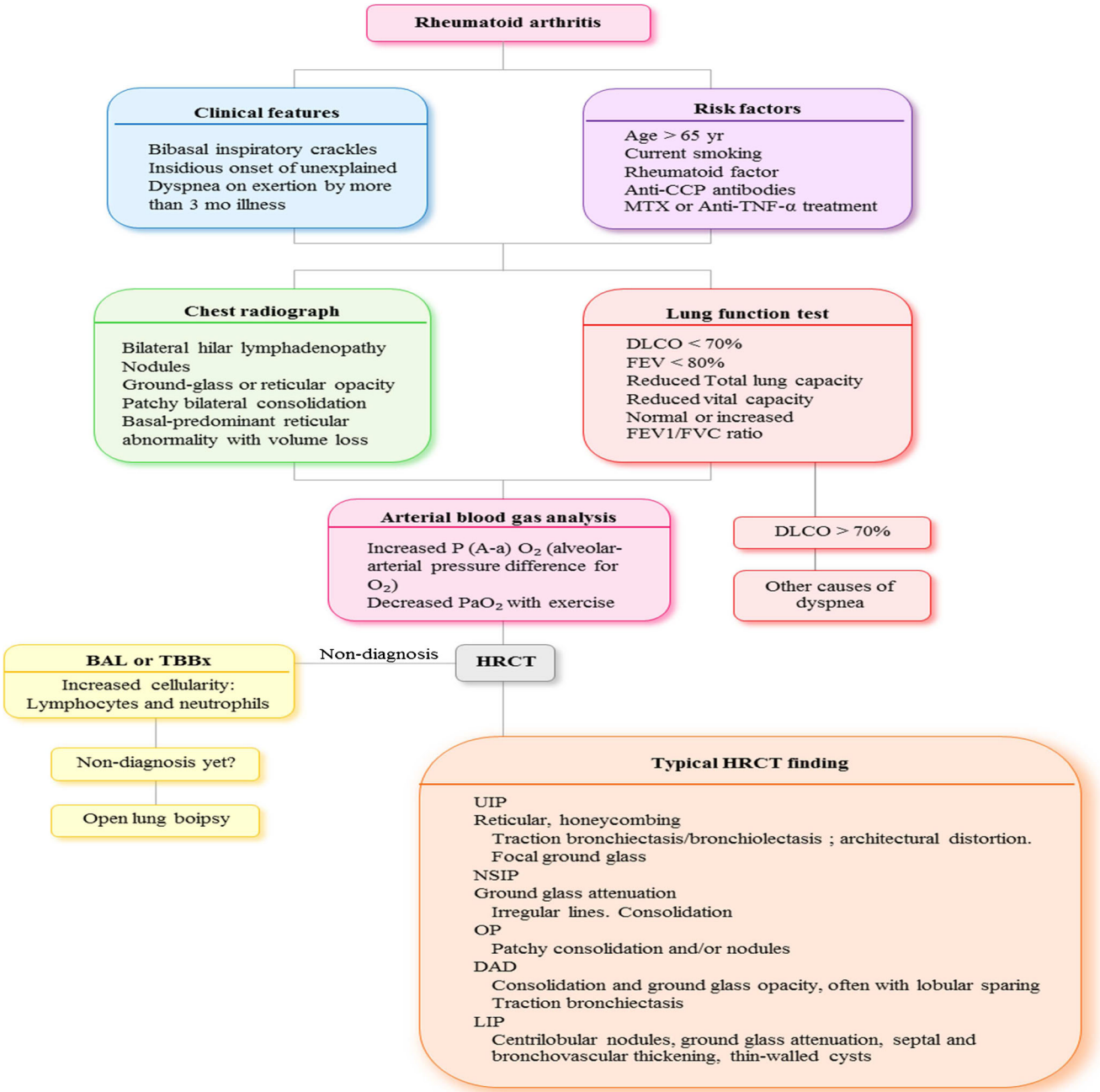

Fig. 1 Diagnosis strategy for the diagnosis of interstitial lung disease in rheumatoid arthritis (*RA-ILD*) [8]. *Anti-CCP* anti-cyclic citrulinated peptide, *Mtx* methotrexate, *Anti-TNF-α* anti-tumor necrosis factor alpha, *DLCO* diffusion capacity of the lung for carbon monoxide, *FEV* forced expiratory volume, *FVC* forced vital capacity, *BAL* bronchoalveolar lavage, *TBBx* transbronchial lung biopsy, *HRCT* high resolution computed tomography, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *DAD* diffuse alveolar damage, *LIP* lymphocytic interstitial pneumonia

Current treatment regimens usually involve corticosteroid therapy (at a dose of 0.5–1 mg/kg with the aim of tapering to a maintenance dose of 10 mg/day or less [4]) with or without an immunosuppressive agent, most commonly, azathioprine [34], mycophenolate mofetil (MMF) [35], or cyclophosphamide [36] based on evidence published from patients treated with connective tissue diseases. Recent retrospective analyses centered on treatment of RA-ILD with MMF and rituximab have shown promising results. In a study of 125 patients with CTD-related ILD treated with MMF, subgroup analysis of 18 patients with RA-ILD identified a trend toward improved forced vital capacity following initiation of therapy. Further, this drug has shown good patient tolerability and safety in patients with CTD-ILD [35]. Retrospective studies with rituximab have recently shown success in cases of refractory CTD-ILD although larger prospective studies are needed to validate these findings

in patients with RA-ILD [37••, 38]. Limited reports also exist for treatment with cyclosporine [39], methotrexate, and tumor necrosis factor (TNF) alpha inhibitors [40, 41]. Response to therapy in RA-ILD seems to correlate with the histopathologic form of the disease. Jani et al suggest routine monitoring of PFTs every 3–6 months in individuals at high risk of progression of RA-ILD in those with UIP pattern on HRCT with >20 % involvement, baseline FVC <60 % of predicted, DLCO <40 % of the predicted, a change in 6–12 months in the FVC ≥10 %, and DLCO ≥15 %. Follow up may be extended to 12 months in patients with low risk of progression in those with non-UIP with <5 % involvement, baseline FVC >90 % predicted, baseline DLCO >80 % predicted, 6–12-month change in FVC ≤5 %, and DLCO ≤5 % [42••]. Low risk as in IIPs, NSIP shows better response to therapy and prognosis than a UIP pattern [23, 43]. The control of joint disease does not correlate with the control of lung disease, and optimal management requires a coordinated approach between an experienced pulmonologist and rheumatologist.

Patients with RA-ILD should be encouraged to refrain from smoking. Smoking-related lung disease should be treated if present. Oxygenation should be evaluated during rest, ambulation, and sleep, and supplemental oxygen should be prescribed as indicated. Vaccinations for influenza and pneumococcal pneumonia are recommended for all patients. In managing the articular manifestations in patients with RA-ILD, methotrexate use should generally be avoided because of well-documented pulmonary toxicity. TNF-alpha inhibitors should be used with caution in these patients following reports of increased rates of lung toxicity with these agents [42••]. In spite of these reports, a prospective observational study of 367 patients with RA-ILD showed no increase in mortality following treatment with anti-TNF agents compared with standard immunomodulatory agents [41]. Patients with progressive disease should be considered for lung transplant evaluation. Survival rates after transplant for RA-ILD are similar to those for IPF and with significant improvements in quality-of-life scores following transplantation [44•].

Conclusion

RA-ILD is the most common pulmonary extra-articular manifestation of RA. Males, old age at the time of diagnosis, and in those with greater RA disease severity are at high risk. Smoking is the independent risk factor. The UIP is the most frequent presentation and has the worst prognosis. Establishing an earlier diagnosis of this complication depends on the level of clinical suspicion and assessment of high-risk patients and progression of the disease. Patients should be stratified according to the risk assessment for outcome of RA-ILD. Assessment of patients should include clinical assessment, PFT, and HRCT which is the standard noninvasive method for diagnosing RA-ILD and correlates with lung biopsy. Surgical biopsy is rarely required in cases of diagnostic uncertainty. The present evidence on treatment of RA-ILD is derived from observational studies or uncontrolled open studies. Corticosteroids are initiated with/without immunosuppressive agents. Refractory cases rituximab may be used. Lung transplant should be considered in progressive disease. Further studies based on well-designed randomized controlled trials are needed to evaluate progression of the disease and evaluate novel therapeutic regimens in RA-ILD.

Compliance with Ethics Guidelines

Conflicts of Interest The author declares that there are no conflicts of interests related to the material.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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