Interstitial lung disease in elderly rheumatoid arthritis patients

Riccardo Messina, Giuliana Guggino, Alida Benfante, Nicola Scichilone

Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy.

Corresponding author: Nicola Scichilone, Piazza delle Cliniche, 2; 90100 Palermo, University of Palermo, Italy; e-mail: nicola.scichilone@unipa.it

Abstract

The increase in life expectancy together with better care of rheumatoid arthritis (RA) has led to higher proportions of elderly individuals with RA. This has challenged the treatment of the disease in older ages, usually characterized by comorbid conditions and polypharmacy. Overall, the lung involvement in RA is present in up to 80% of **patients** ~~subjects~~, **depending on the assessment tools used, and** ~~mainly with features of~~ interstitial abnormalities **are among the most common**: when present, interstitial lung disease (ILD) worsens the prognosis of RA, being the second most common cause of mortality. The aged lung undergoes functional and structural changes termed immunosenescence and inflammaging, which facilitate the occurrence of fibrosis of the lung. Therefore, ILD tends to occur more frequently in older patients with RA. The age at onset of RA distinguishes ~~subjects~~ **patients** in young-onset RA (YORA, <60 yrs) and late-onset RA (LORA, >60 yrs); the latter are characterized by more severe features of the disease and higher rates of lung involvement. The most frequent RA-related ILD radiological pattern is the usual interstitial pneumonia (UIP); this includes peripheral and basal predominant reticulation and honeycombing with or without associated traction bronchiectasis. ~~Subjects~~ **Patients** with the UIP pattern are usually older and with more rapid decline in lung function and worse prognosis. Treatment with corticosteroids in elderly patients carries the risk of adverse effects, such as osteoporosis, infections, diabetes, peptic ulcers, and cataract. The use of disease-modifying antirheumatic drugs (DMARDs) is well-tolerated by the elderly. The current narrative review aims at elucidating the association between ILD and RA in older individuals.

Key points:

- The aged lung is characterized by changes in the function of epithelial cells and fibroblasts, as part of the immunosenescence and inflammaging processes, wich facilitate profibrotic abnormalities.

- RA is steadily increasing in the elderly because patients live longer due to a better management of comorbilities that have increased in life expectancy. This phenomenon has contributed to higher number of patients are diagnosed with late-onset RA. This form is characterized by more severe joint and extra-articular features of disease.

- The lung involvement is frequent in patients with RA, mostly affecting the interstitial component, and the prevalence increases with aging. In addition, advanced age is the most significant predictor of poor lung prognosis.

- Age at disease onset impacts on prognosis. Treatment with corticosteroids in elderly patients carries the risk of adverse effects, such as osteoporosis, infection, diabetes, peptic ulcers, cataract, whereas treatment with DMARDs is well-tolerated by the elderly. In older ~~subjects~~ **patients** with frequent comorbidities, the most suitable therapy should take into account the potential involvement of other organs.

Running heading: Lung involvement in older rheumatoid arthritis patients

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1. Introduction: ageing and the lung in Rheumatoid Arthritis (RA)

Although the pivotal clinical feature of RA is inflammation of the synovial lining of joints, RA is characterized by several extra-articular manifestations. Lung disease is a major contributor to the extra-articular morbidity, occurring up to 80% of RA patients [13-16]; and may result directly from RA involvement or secondary to immune-modulating medications used to treat RA, due to opportunistic infection and drug toxicity [17]. Lung disease often occurs within the first 5 years of disease [9,18] but may precede articular symptoms in up to 20% of cases characterized by respiratory symptoms [19,20].

The increases in life expectancy has led to higher proportions of elderly individuals, aged 65 and above, representing over 2 billion people worldwide, outnumbering younger individuals [1]. As a consequence, the incidence and prevalence of age-related diseases has dramatically increased, and there is evidence that structural changes of the lung components could facilitate the occurrence of lung diseases, such as those characterized by altered connective tissue. Indeed, physiologic changes to the lungs contribute to changes in lung function and susceptibility to disease. In this regard, age-related processes such as immunosenescence, the immune system dysfunctions occurring with aging [2], and inflammaging, a form of chronic, sterile, low-grade inflammation that develops with ageing, are supposed to diminish the regenerative capacity of the aged lung and seem to play a central role in lung fibrosis [3]. Alveolar epithelial cells and fibroblasts have been shown to undergo age-related abnormalities that could contribute to development of lung fibrosis [4]. The extracellular matrix (ECM) of aging lungs expresses a profibrotic phenotype characterized by increased Type I and III collagen and TGF-b1 expression [5]. Impaired autophagy and mitochondrial dysfunction, as part of immunosenescence, may

contribute to fibrosis of the lung. The lung involvement is a common complication of rheumatoid arthritis (RA), and the ~~second~~ **third** commonest cause of mortality [6-11].

The steadily **increasing incidence** of RA among the elderly has been attributed to two main factors: a) patients with RA live longer due to better management; and b) an increasing number of patients are being diagnosed with elderly-onset RA. Some studies categorize RA by a threshold set at age 60: young-onset RA (YORA, <60 yrs) and late-onset RA (LORA, >60 yrs) van der Heijde DM, van Riel PL, van Leeuwen MA, et al. Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective followup study of early rheumatoid arthritis, J Rheumatol , 1991, vol. 18 (pg. 1285-9); Deal CL, Meenan RF, Goldenberg DL, et al. The clinical features of elderly-onset rheumatoid arthritis. A comparison with younger-onset disease of similar duration, Arthritis Rheum , 1985, vol. 28 (pg. 987-94), Pease CT, Bhakta BB, Devlin J, et al. Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors, Rheumatology , 1999, vol. 38 (pg. 228-34). Depending on the specific population observed, complications increase with increasing age and older patients have more joint erosions [12]. Hereafter, we present a narrative review of the literature on the influence of age in the relationship between interstitial lung disease (ILD) and RA. In particular, we explored to what extent ILD occurs in RA individuals, and what are the clinical consequences in older **patients** ~~subjects~~. Given the scope of the paper and the paucity of data on the topic, a relevant paragraph was dedicated to the unexplored areas and unanswered questions.

2. RA and lung diseases

~~Although the pivotal clinical feature of RA is inflammation of the synovial lining of joints, RA is characterized by several extra-articular manifestations. Lung disease is a major contributor to the~~

~~extra-articular morbidity, occurring up to 80% of RA patients [13-16]; and may result directly from RA involvement or secondary to immune-modulating medications used to treat RA, due to opportunistic infection and drug toxicity [17]. Lung disease often occurs within the first 5 years of disease [9,18] but may precede articular symptoms in up to 20% of cases characterized by respiratory symptoms [19,20].~~

All components of the lungs have been shown to be involved (Table 1). ILD is the most frequent pulmonary involvement associated with RA [21]. The prevalence of RA-related ILD ranges from 1% to 58% in different studies, according to the diagnostic tecnique used and to the population studied [10,22,23]. In addition, studies showed that patients with RA who underwent a screening procedure regardless of the presence of respiratory symptoms often presented with radiologic abnormalities on HRCT, referred to as interstitial lung abnormalities. Thus, RA-ILD is often under-recognized and in at least 30% of patients remains subclinical [22,24]. Gabbay et al identified the male gender as the only risk factor for the presence of abnormalities compatible with ILD. The explanation for the male preponderance is unclear but it was not associated with age [22].

Despite the improvements in RA therapy, the incidence of ILD has remained fairly stable, whereas the rate of other extra-articular manifestations of RA has decreased [11]. Although RA is more prevalent in females, ILD-RA is more common in male patients, with a male to female ratio of 2:1 [25,26]. Several risk factors have been identified for the development of RA-ILD, including older age [8,27], late-onset RA and longer disease duration. Onset of lung disease typically occurs in the fifth and sixth decades of life [11]. In addition, advanced age seems to correlate with increased risk of acute exacerbation (AE) of ILD. Hozumi et al [28] found that the median age of study

population at the time of diagnosis of RA-ILD was 62 years (range 31-83 yrs), and that median age at the onset of AE was 72 years (range 60-86 yrs).

3. Clinical and radiological presentations of ILD in RA

In ~~subjects~~ **patients** affected by RA-ILD, the most common symptoms are exertional dyspnea and non productive cough. At physical examination tachypnea and bibasilar inspiratory crackles are very common. Clubbing occurs frequently in patients with RA-related ILD characterized by UIP pattern at HRCT. This sign is significantly less common in those with other HRCT patterns of RA-related ILD [29]. Cyanosis, edema, and signs of pulmonary hypertension (PH) may also occur in advanced phases of disease. In majority of patients with RA-related ILD, pulmonary function tests may shown a restrictive ventilatory defect with reduction in total lung capacity (TLC) and forced vital capacity (FVC) with or without decreased diffusing capacity of the lung for carbon monoxide (DLCO). It has been demonstrated that DLCO is highly sensitive for predicting the presence of ILD [38]. Gabbay et al [22] conducted a study with the aim to determine the prevalence of ILD associated with RA, using different sensitive techniques in patients with joint disease of less than 2-yr duration. The Authors showed that in the 33% of patients with early RA, DLCO was < 80% of predicted and able to predict the presence of ILD. Abnormal lung function may include oxygen desaturation during the 6-minute walk test (6MWT). Desaturation < 88% is associated with a worse prognosis in ILD and is useful for guiding need for oxygen therapy. Moreover, the impairment of FVC and DLCO at baseline is associated with poorer prognosis, and FVC <60% and DLCO <40% of predicted values at baseline are independent predictors of mortality. In addition, similarly to IPF, a decrease in FVC of ≥10% or a decrease in the DLCO of ≥15% over 6–12 months is considered clinically relevant and associated with increased mortality [30,31].

Several studies have confirmed that the most common radiological and pathological pattern in RA-ILD is the UIP pattern (Figure 1) [32] compared to other forms of connective tissue disease-related ILD, such as systemic sclerosis, idiopathic inflammatory myositis, dermatomyositis, Sjögren's syndrome, undifferentiated connective tissue disease), in which the non specific interstitial pneumonia (NSIP) pattern is the most frequent [33,34]. Interestingly, patients with RA-ILD with UIP pattern are more frequently older males [20, 21], current or former smokers, and have more respiratory system–related hospitalizations and worse prognosis than those with a non-UIP pattern [21, 35], although the clinical course of RA-related UIP is highly variable [28]. ILD is second only to cardiac disease as a cause of mortality in patients with RA [6-11]. Moreover, ILD-associated pulmonary hypertension (PH) may contribute to the high incidence of cardiovascular disease–related deaths in patients with RA [22]. In this regard, advanced age and longe disease duration are the most significant predictors of poor prognosis [36]. Other relevant factors associated with higher mortality are male sex, the extent of fibrosis and the UIP pattern evaluated by HRCT, the severity of lung function impairment in terms of DLCO and FVC, AE and RA activity [37-40].

In a proportion of RA **patients** ~~subjects~~ it is possible to demonstrate a combined pulmonary fibrosis and emphysema (CPFE) state on HRCT scans, identified by upper lobe emphysema and lower lobe fibrosis. Patients with CPFE are more frequently older, male and with a heavy smoking history. CPFE syndrome is characterized by severe dyspnoea, presereved lung volume, severely impaired DLCO, and is also associated with an increased risk of pulmonary hypertension [41].

The **diagnostic** approach with a multidisciplinary team (MDT), including pulmonologist, radiologist and, in selected cases, pathologist, is mandatory for the diagnosis and management of ILD [42]. ILD is a common complication in the connective tissue disease (CTD) and although occurs in patients with already identified pathology, it can also be the first manifestation of previously unrecognized disease or may occur years prior to the disease diagnosis [43]. Futhermore, a new

term, “interstitial pneumonia with autoimmune features” (IPAF) has been proposed to describe interstitial lung involvement and features suggestive of underlying systemic autoimmune disease which do not meet current criteria for a specific CTD [44], making the rheumatological assessment increasingly important. In a recent study, Levi Y et al assessed the effect of adding a rheumatologist to the MDT for routine rheumatology assessment, showing an increase diagnostic accuracy and a reducing use of invasive procedures [45]. Although not always feasible, the evaluation of patients with suspected autoimmune features by a rheumatologist and ILD expert is desirable [46]. Little is known with regard to the features of elderly patients in the context of MDT assessment. Taking into consideration the age-related alterations of the lung and the potential interaction of respiratory and non respiratory drugs are mandatory steps.

4. Treatment of RA-ILD according to age

Elderly RA patients do not receive the same treatment as younger RA patients, prevalently due to concomitant age-related diseases, suggesting that age at the onset of RA influences prognosis and any treatment prescribed. Frequently, YORA patients receive an early treatment with DMARDs and biologics whereas LORA patients are treated more often with corticosteroids. Therefore, age at disease onset influences the choice of pharmacological treatment. The high number of comorbidities and coexisting diseases requires treatment with other drugs; however, when comorbidity at baseline was also taken into account, the choice of treatment was associated with age at onset of disease [47]. The rapid relief of symptoms achieved with corticosteroid treatment and the potential side effects of DMARDs in older patients can influence the therapeutic decisions. Treatment with corticosteroids in elderly patients is not free of adverse effects (such as osteoporosis, infection, diabetes, peptic ulcers, cataract) [48] and several studies have shown that

treatment with DMARDs is well-tolerated by the elderly [49,50]. Despite it, risk factors for adverse effects should be evaluated carefully before starting any therapy in the elderly [51,52].

No international guidelines are available on the management of RA-ILD because of limited evidence. **The multidisciplinary approach is important in the management of RA-ILD and should include pulmonologist, rheumatologist and even cardiologist as well as allied health professionals.** In clinical practice, before starting any treatment the severity of the disease should be evaluated by clinical, functional and radiological assessments. In addition, the risks and benefits of therapy for each patient should be addressed. Contrary to IPF, in which immunosuppressive therapy combined with glucocorticoids resulted in a strong recommendation against its use [53], treatment with anti-inflammatory and/or immunosuppressive agents is in place for RA-ILD. In a longitudinal retrospective study on connective tissue disease-associated ILD, 125 subjects, including 18 patients with RA-related ILD, were enrolled with the aim to assess efficacy and safety of mycophenolate mofetil (MMF). MMF combined with a low dose of prednisone showed an improvement in lung functional parameters (FVC and DLCO) in the subgroup of patients with an RA-associated non-UIP pattern, and a stabilization of these parameters in patients with the UIP pattern. Moreover, MMF proved to be well tolerated by patients with a median of treatment of 897 days and with a discontinuation rate due to adverse events of less than 10% [54]. The mean age in the enrolled subjects was 60.4 ± 11.6 year (mean ± SD); however, no specific analysis was performed to address the impact of age on the efficacy and safety of MMF.

Rituximab (RTX) is a chimeric monoclonal antibody targeting the cell-surface receptor CD20 found on B cells. Treatment with RTX leads to B cell depletion and reduction of autoantibody generation. RTX is known to be effective in the treatment of articular manifestations in RA and some studies

reports improvement in ILD associated with connective tissue disorders [55]. A potential toxic effect of RTX on the lung has been hypothesized [56]. Yusof et al [57] conducted a single centre observational study for >10 years to evaluate the effect of RTX in patients with RA-ILD. Of 700 RA-patients treated with RTX, 56 received a diagnosis of ILD. Most patients with RA-ILD treated with RTX remained stable or improved after treatment over a prolonged follow-up period. In this subgroup of patients, the median age was 63 years (range 59-68 years). Interestingly, patients who developed a worsening of lung function or death during the study were older with a median age of 70 years (range 61-73 years). Fui et al [58] recently described the clinical and radiological characteristics of 28 patients with RA-ILD (mean age 66.2 ± 11.3 yrs) and the efficacy of anti-CD20 therapy in 14 patients who had undergone RTX therapy for 1 year due to the worsening of the interstitial lung involvement. HRCT features revealed UIP in 15/28 of patients and NSIP in 8/28 patients; other radiological patterns were nodular ILD (4/28) and pleuro-parenchymal fibroelastosis (1/28). No specific analysis by age was conducted.

Methotrexate (MTX), commonly used as first-line disease-modifying treatment in RA joint disease [59] is able to improve overall survival in patients affected by AR [60]. However, MTX has been demonstrated to induce lung toxicity in patients affected by RA. In clinical practice, differentiating MTX-induced lung toxicity from the RA-related lung disease is crucial to avoid the discontinuation of such important treatment [61]. Sathi et al [62] conducted a large prospective study recruiting 223 patients, with 154 subjects affected by RA. All recruited patients had started low-dose MTX and were followed for 2 years or until development of MTX-related pneumonitis (MTX-P). The rate of patients who developed pneumonitis was 1%. The Authors were unable to identify any risk factor linked to the occurrence of MTX-P. In a multicenter case-control study [63], risk factors for

MTX-induced lung injury were assessed in patients with RA. Older age was among the strongest predictors of lung injury

The anti-tumor necrosis factor alpha (anti-TNFα) drugs like infliximab, etanercept, adalimumab, certolizumab and golimumab approved for the treatment of RA, are considered the most effective therapeutic option in the disease, especially when used to treat patients with early onset disease or high disease activity [64]. However, the possible occurrence of new onset or exacerbation of ILD associated with their use has been hypothesized. Perez-Alvarez and co-workes [65] collected data about 122 cases of new onset or exacerbation of ILD, including 108 patients with RA, secondary to administration of biologic therapies (58 etanercept, 56 infliximab, 3 adalimumab and 5 rituximab). The lung involvement occurred after a mean of 26 weeks of treatment with biologic agents, and seems to be correlated with a preexisting or underlying pulmonary disease, especially in older patients with age >65 years.

5. Unexplored areas and unanswered questions in the elderly

The findings of the current narrative review based on available literature points out that ILD is frequently observed in older individuals affected by RA, affecting the clinical course of the disease and worsening the prognosis. This advocates for early recognition of the lung involvement and treatment. To date, there is no specific treatment for lung fibrosis secondary to connective diseases; however, studies on the efficacy of antifibrotic agents in autoimmune connective diseases are ongoing, and findings should be available soon. In this regard, there is no reason why these drugs should be limited to younger patients.

Restrictive inclusion and exclusion criteria are usually applied to enrol the volunteers of the RCTs, with the aim to exclude potential confounding factors that may affect the results. Older age and comorbidities are the most often used exclusion criteria. As a consequence, the applicability of the findings from RCTs in daily clinical practice is strongly limited. Thus, specifically designed studies to assess safety and efficacy of drugs in elderly subjects suffering from comorbid conditions are advocated.

Figure Legend

Fig 1 a-b: Computed tomography scans of rheumatoid nodule (arrow) and interstitial lung disease in a 70 year old man affected by rheumatoid arthritis.

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