Article:
Kelly, C, Emery, P orcid.org/0000-0002-7429-8482 and Dieudé, P (2021) Current issues in rheumatoid arthritis associated interstitial lung disease. The Lancet Rheumatology, 3 (11). E798-E807. ISSN 2665-9913

https://doi.org/10.1016/S2665-9913(21)00250-2

CURRENT ISSUES IN RHEUMATOID ARTHRITIS ASSOCIATED INTERSTITIAL LUNG DISEASE (RA-ILD)

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Key words: Rheumatoid arthritis (RA); Interstitial lung disease (ILD); mortality; screening; monitoring; therapeutics; intervention.

ABSTRACT

Rheumatoid arthritis (RA) is associated with a ten-fold increased risk of interstitial lung disease (ILD). The presence of ILD in a patient with RA influences both prognosis and the choice of therapeutic intervention. Although there has been increasing recent awareness of the relevance of ILD to the outcome for RA patients, there remains limited consensus around several important aspects of disease diagnosis and management. This review highlights two of the main areas where a much greater standardisation of approach is urgently indicated. Firstly, the development of a screening approach based on established risk factors is a priority. It is essential we learn how to identify patients with RA-ILD early and then monitor their condition to assess progression and measure the potential influence of therapeutic intervention. Secondly, we require to consolidate the therapeutic evidence base to agree a standard approach to intervention. Although we already have a range of potentially effective

treatments, further clinical trials are required to define the optimal stratification for therapeutic intervention.

INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune inflammatory disorder which can target many organs and has a worldwide prevalence approaching 1%. Although the synovium is usually the first tissue to be involved, many other tissues can become affected. Pulmonary disease especially is increasingly recognised as a life-threatening complication of RA, with clinically relevant interstitial lung disease (ILD) reported to have a lifetime prevalence of 7.7% in RA, associated with a marked reduction in life expectancy [1]. Currently there is no agreement on exactly how to predict which RA patients will develop lung involvement, although the range of risk factors for ILD in RA are increasingly well recognised. Early diagnosis is essential, as is effective monitoring of disease progression. A quarter of all patients with RA-ILD presently have severe impairment of lung function at baseline and a further 25% develop this in the first five years following diagnosis [2]. The lack of consensus around both screening for, and monitoring the progression of, RA-ILD needs to be urgently addressed if we are to select appropriate patients for early therapeutic intervention.

High resolution computed tomography (HRCT) of the thorax is accepted as the gold-standard approach for diagnosis of ILD. Now that clinicians have access to a wider range of potential pharmacological interventions in RA, it is essential that we recognise which drugs to use and when to administer them in the context of co-existent ILD. Presently, therapeutic selection is largely empiric, although there is increasing recognition of the need to standardise our approach. A clear distinction is needed between those patients whose ILD is asymptomatic and stable and those who have progressive disease with associated cough and dyspnoea. Choice of therapy in the first group focusses on the selection of drugs capable of improving articular disease without triggering deterioration in pulmonary features, whereas patients with progressive pulmonary disease require agents that reverse or stabilise this process. Among those with progressive ILD, patients with an inflammatory pattern appear to have a better prognosis and often respond to immunosuppressive therapy and certain biologic agents, while patients with progressive pulmonary fibrosis will often require the addition of anti-fibrotic therapy to reduce the rate of deterioration.

This first part of this review attempts to define the issue of which RA patients to screen by describing the present state of knowledge around established risk factors for ILD. It describes some potential markers of disease progression and touches upon the timing of, and mechanisms for, both screening and monitoring. It identifies present unmet needs and calls for international collaboration to improve and standardise the detection of ILD in RA. The second part of the review summarises the level of therapeutic information that currently exists to inform the management of RA-ILD. It highlights the need for standardisation of strategies for therapeutic intervention, dependent upon disease subtype and extent. It emphasises the urgent requirement for further international studies, ideally involving large double-blind

randomised comparisons conducted across a wide geographic area, to consolidate the present limited evidence-base and advise and inform future therapeutic stratification.

1 SCREENING

Screening for rheumatoid arthritis-associated Interstitial lung disease (RA-ILD) involves answering 3 challenging questions: Who? When? and How? The answer to 'Who' requires the identification of risk factors for clinical and preclinical RA-ILD. Ideally, risk factors need to be identified for specific subtypes of ILD identified by high-resolution CT (HRCT). The patterns of usual interstitial pneumonia (UIP), non-UIP, progressive ILD and progressive preclinical ILD all require different therapeutic interventions. 'When' involves identifying the optimal time for screening ILD among patients with RA: those with the highest probability of incidental RA-ILD. Lastly, 'How' implies selecting the best tool for identifying most patients with RA-ILD, including those with asymptomatic ILD (*i.e.* a test with a high sensitivity) (Figure 1).

WHO?

Improving ILD risk stratification in patients with RA

The relatively high prevalence of preclinical ILD seen on chest HRCT scan in patients with RA shows that screening based on only clinical symptoms is ineffective because of the poor sensitivity [1-3]. We require the identification of risk factors that allow for stratifying patients with RA who are considered at high risk of ILD. Principal risk factors can be divided into 2 main categories: i) individual risk factors (sex, age, genetic background and environmental factors) and ii) risk factors related to the underlying chronic inflammatory arthritis (specific sub-phenotypes, disease activity and related specific treatments).

Most studies that examined risk factors for RA-ILD have several limitations, limiting conclusions and producing discrepancies. These limitations include differing definitions of RA-ILD (clinical, chest radiography, HRCT) and controls (healthy individuals, patients with RA without clinical ILD, patients with RA without HRCT-proven ILD). In addition, most of these studies considered RA-ILD as a homogeneous entity rather than a heterogenous condition that includes different subtypes as defined by chest HRCT scan. It is especially important to differentiate usual interstitial pneumonia (UIP) from other non-UIP patterns.

Individual risk factors

Male sex and older age are demographic factors usually associated with RA-ILD [1, 3, 4]; these are also shared by idiopathic pulmonary fibrosis (IPF), which illustrates the numerous similarities between RA-ILD and IPF. Men with RA have a two-fold increased risk of ILD.[2] Older age is associated with RA-ILD [1, 3], suggesting that immune-senescence might be relevant. Recent findings of rare variants in telomere maintenance genes in patients with RA-ILD strengthens this hypothesis [5]. Although the role of aging in RA-ILD remains to be clarified, 2 large multi-ethnic case-control association studies found delayed onset of RA of up to 10 years in patients with ILD [6, 7]. In a recent case-control study, obesity was associated with a two-fold increase in ILD in the RA population [8].

Cigarette smoking, a risk factor for RA itself, also increases the risk of ILD with RA, with a dose-effect relationship [3, 9], and is also a risk factor for IPF [10]. However, the link between cigarette smoking and risk of ILD in the RA population was not observed in a large multi-ethnic study [6]. In addition, a recent case–control study within the BRASS did not find a contribution of cumulative past smoking, whereas current smoking was associated with more than three-fold increased risk of incident RA-ILD [8]. These findings indicate the need for future prospective studies to better understand the exact role of cigarette smoking in the risk of incident ILD in the RA population.

The high prevalence of UIP in RA-ILD and the risk factors in common both support the hypothesis of a shared genetic background between RA-ILD and IPF. Excess rare variants were found in telomere maintenance genes and in *SFTPC,* involved in surfactant homeostasis, with increased odds ratio of 3.17 against controls [5]. However, a major limitation was the lack of RA patients without ILD as controls, which therefore cannot exclude the possible contribution of these rare variants to overall RA susceptibility. The functional *MUC5B* rs35705950 promoter variant, the major risk factor for IPF, was recently identified as a risk factor for RA-ILD in a large multi-ethnic case-control association study including patients with RA without ILD as controls; these findings provide definitive evidence for a common genetic architecture in RA-ILD and IPF [6, 11]. Of interest, the association between this variant and RA-ILD was restricted to patients with RA-UIP [6]. These findings led to the identification of a major RA-ILD risk factor; patients carrying the *MUC5B* risk allele had more than 3- and 6-fold increased risks of ILD and UIP, respectively [6]. A case–control genetic association study of a Japanese population, found an association between *HLA-DRB1*1502* carriage and RA-ILD [12]. However, a recent intra-case genome-wide association study, performed in the same population comparing RA patients with and without ILD, did not find a significant association between RA-ILD and the *HLA-DRB1* locus [13], so the exact contribution of the *HLA-DRB1* locus to the RA-ILD susceptibility remains unclear.

RA-related risk factors

Over the last decade, interest in identifying RA phenotypical markers associated with RA-ILD has increased. The association between RA-ILD and RA-specific antibodies (*i.e.,* rheumatoid factor and anti-citrullinated protein antibodies [ACPA]) is controversial. Seropositivity for these autoantibodies has been linked to a more severe RA course and increased risk of extra-articular manifestations. Several retrospective studies have reported increased risk of RA-ILD with rheumatoid factor and/or ACPA seropositivity and/or high titres of autoantibodies [3, 9]. A meta-analysis also revealed the association between ACPA positivity and RA-ILD [14]. However, 2 recent large multi-ethnic case-control studies did not find this association with high ACPA prevalence in both groups [6, 7]. This discrepancy regarding the role of ACPA-positive status may have several explanations. These studies avoided misclassification by defining the RA-without-ILD control group with chest HRCT. Also, the 2010 ACR/EULAR criteria for RA in which seropositivity for ACPA is required, could be confounding. In agreement with the paradigm of a breach in immune tolerance to citrullinated self-proteins in the lung, numerous studies have demonstrated increased ACPA titres in patients with RA-ILD, thus suggesting that high titres could be more relevant than positive status [3, 15]. Finally, the roles of other ACPAs, anti-carbamylated proteins and anti-malondialdehyde-acetaldehyde antibodies, are being explored within ILD risk stratification in RA [16, 17].

As for other extra-articular manifestations of RA, disease activity may also increase the risk of ILD. In line with this, prednisone use could be considered a surrogate marker of active RA [18] as is an elevated erythrocyte sedimentation rate [9] and both were reported as risk factors for RA-ILD. The definitive evidence for a link between RA activity and risk of incident ILD arose from a prospective cohort study reporting that for each unit increase in RA Disease Activity Score in 28 joints, the risk of RA-ILD increased by 35% [19]. These findings suggest that RA activity contributes to the risk of occurrence of ILD, which raises the question of the potential role of disease modifying anti-rheumatic drugs (DMARDs) and both treat-to-target and tight control strategies in preventing or delaying ILD in patients with RA. To our knowledge, the role of both treat-to-target and tight control strategies in the risk of RA-ILD has not yet been specifically investigated.

Risk factors for progressive RA-ILD

Almost 50% of patients with RA-ILD will have progressive disease [2]. No adequately randomized trials have yet provided recommendations for managing progressive symptomatic RA-ILD. Limited studies have examined risk factors for progressive RA-ILD. The UIP pattern is usually linked to more progressive disease and high mortality as compared with non-UIP patterns [20]. In a retrospective study of 137 patients with RA-ILD, with progressive ILD defined as diffusing capacity for carbon monoxide (DLCO) <40% and forced vital capacity (FVC) <50%, lower DLCO and FVC at baseline increased the risk for progression to DLCO <40% predicted and FVC <50% predicted. Rapid early decline was associated with increased risk of progression [19]. A retrospective study of 64 RA-ILD patients reported radiographic progression correlated with HRCT extent at baseline, replicating previous findings [21]. Lastly, a small study of RA-ILD patients with progressive disease suggested serum KL-6 level was a significant predictor of RA-ILD progression [22]. These risk factors apply to patients with clinical RA-ILD and are not relevant prior to the detection of ILD.

Risk factors for pre-clinical RA-ILD

Clinically significant RA-ILD will occur in almost 10% of patients with RA [1, 23]. However, multiple cross-sectional studies using HRCT have identified preclinical ILD in up to 50% of RA patients [4, 24, 25]. Nonetheless, there is limited knowledge about the factors that may predict risk of preclinical RA-ILD progression of ILD and most of the cited studies included relatively small numbers. Several serum biomarkers that are direct or surrogate biomarkers of ILD without specificity for RA-ILD, such as plasma surfactant protein-D, matrix metalloproteinase-7 [26], CA-125 [27] and KL-6 [22], were associated with RA-ILD and could be of interest for screening preclinical RA-ILD. Cross-sectional studies of preclinical RA-ILD in a large population are needed. Table 1 summarises the risk factors for RA-ILD.

WHEN?

The exact prevalence and incidence of RA-ILD are poorly defined because of little consensus regarding i) definition of RA-ILD, ii) detection of RA-ILD and iii) appropriate timing of screening (*i.e*. RA duration). Long RA duration has been found a risk factor for incident RA-ILD [28]. The RA duration at ILD diagnosis is highly variable, depending on the definition of RA-ILD used and the methods of detection. Consequently, the identification of the optimal time for screening

ILD in patients with RA remains unknown. However, given the cumulative nature of all measures of damage in patients with RA, early identification and targeted intervention based on prognostic factors would be predicted to produce the optimal chance of success.

HOW?

Early detection of RA-ILD may affect treatment strategy. The relatively high prevalence of preclinical HRCT-detected ILD in patients with RA suggests that screening based on clinical symptoms has poor sensitivity [4, 24, 25]. Chest HRCT is currently the gold standard for diagnosis, offering both quantitative (extent) and qualitative (subtype) evaluation. Indeed, HRCT findings offer good correlation with the histological pattern [29]. Nonetheless, systematic screening for ILD with HRCT is not appropriate because of the exposure to ionizing radiation and its lack of proven cost-effectiveness. Therefore, a relevant screening test requires high sensitivity to optimise the detection of individuals eligible for a chest HRCT scan.

Although rheumatologists frequently use pulmonary function tests as a screening tool for RA-ILD for their patients with systemic sclerosis, they lack sensitivity for detecting ILD in such patients [30]. Extrapolation to RA-ILD would suggest that pulmonary function tests alone are inadequate screening tools for RA-ILD. Recently, the velcro sound detector, a non-invasive technique that identifies velcro crackles in respiratory sounds recorded with an electronic stethoscope, was developed to help identify early RA-ILD. In an Italian multi-centre study including patients without symptoms, velcro sound detection predicted the presence of HRCT-defined ILD with 93% sensitivity [31]. Lung ultrasonography (US) has also been developed in connective tissue disease related ILD. A recent meta-analysis of prospective studies evaluating lung ultrasonography in connective tissue disease-related ILD included 266 with RA-ILD and reported a pooled sensitivity of 86% [32]. Dedicated research is needed to determine the place of ultrasonography and Velcro sound detection in RA-ILD screening.

There are still many remaining questions regarding the natural history of RA-ILD, the lack of consensus for a screening strategy definition, and the development of a composite index for both the diagnosis and prognosis of RA-ILD. However, with reference to the current state of knowledge of screening for RA-ILD (Figure 2), the following detection strategy could be projected: patients with RA at high risk of ILD occurrence could be screening for preclinical ILD using lung US and/or electronic stethoscope to detect preclinical ILD. Those patients identified as having preclinical RA-ILD would be evaluated with chest HRCT scan and PFTs and then referred to a pulmonologist (Figure 3). Several questions remain unanswered; which patients at high risk of RA-ILD should be screened with HRCT? Should reassessment be conducted and if so, at what interval? (Figure 3). Presently, recommendations are lacking on the Who, When and How of screening for RA-ILD. These unmet needs indicate the need for international collaboration to improve the detection and inform the management of RA-ILD.

2 THERAPEUTIC ISSUES

It seems sensible to consider the approach to therapeutic intervention in patients with RA-ILD as two distinct issues. Firstly, which drugs are the best options in RA-ILD patients whose articular disease is the dominant clinical concern? Secondly, which therapeutic agents can positively influence outcome for RA-ILD patients whose lung disease is their major issue?

WHICH DRUGS TO USE FOR ARTICULAR DISEASE IN PATIENTS WITH RA-ILD

Patients with mild to moderate articular disease

The main aims of treatment of articular disease are to reduce disease activity and improve patient function. Disease activity is assessed by a composite calculation including swelling and tenderness across 28 joints (DAS28 score). Clinicians aim to treat to achieve a target DAS28 score of under 2.6. Traditional disease modifying anti-rheumatic drugs (DMARDs) still form the basis for therapeutic intervention in most RA patients. Methotrexate is considered the 'gold standard' DMARD and is the anchor drug for most patients who require combination therapy with more than one agent. However, for many years it was considered ill-advised to use methotrexate in RA patients with co-existent ILD because of the perceived risk of exacerbating lung damage. More recently, it has been conclusively demonstrated that methotrexate does not exacerbate ILD [33] and indeed that it probably improves rather than reduces survival in patients with RA-ILD [6]. Whilst methotrexate can cause fatal hypersensitivity pneumonitis in susceptible individuals, this is now relatively rare following the widespread adoption of measuring lung function as a prelude to commencing methotrexate. Whilst it is still reasonable to consider alternatives to methotrexate in patients with a reduction in baseline vital capacity below 70%, or gas transfer under 60% predicted, as acute pneumonitis in patients with reduced pulmonary reserve is more likely to be fatal, the presence or development of mild or stable ILD does not of itself require methotrexate to be avoided or discontinued in most RA patients. Indeed, recommendations now encourage continuation of methotrexate in the presence of RA-ILD unless it is sufficiently severe or progressive to require treatment in its own right [34].

Leflunomide is an alternative DMARD to methotrexate for RA, and the two have been successfully used in combination, although not licensed for this. Although leflunomide has also been associated with hypersensitivity pneumonitis [35], this has been reported most often among patients of Asian origin [36] and appears rare in Caucasians. Indeed, a recent report describes the benefit of leflunomide in treating chronic hypersensitivity pneumonitis in non-RA patients providing they did not have established fibrosis [37]. Again, it is now recommended that leflunomide therapy can also be maintained in patients with stable or mild RA-ILD [34]. Other conventional DMARDs have not been shown to have any significant impact on the development or progression of RA-ILD and there appears to be no justification for their discontinuation in this setting. Combinations of standard DMARDs should be used in the same way for patients with RA-ILD as for those with RA alone. If the articular response is inadequate, as assessed by objective measures such as the disease activity score in 28 joints (DAS28), then escalation to biologic therapy should be considered.

If DMARDs alone or in combination fail to achieve a response and the DAS28 score remains above 5.1 for 6 months or more, clinicians in the United Kingdom should consider the use of a biologic agent. The threshold for such intervention is considerably lower in the United States and in several European countries, while biologics may not be available at all in some developing countries. Biologic drugs include anti-tumour necrosis factor (anti-TNF) agents but there are now a considerable range of other effective biologic agents available for the treatment of RA. The influence of different biologics on ILD varies considerably and this has become an area of great interest and relevance.

Patients with severe articular disease

Anti-TNF agents have used in the treatment of RA for over 20 years. Many reports of the development or exacerbation of ILD soon emerged, leading to the British Society of Rheumatology (BSR) advising against their use in patients with RA-ILD [38]. A Japanese study confirmed a high prevalence of worsening ILD among patients treated with each of the 3 main anti-TNF drugs, which was not seen among RA-ILD patients treated with either tocilizumab or abatacept [39]. However, in the only available prospective study, no deterioration was seen over one year in 42 RA-ILD patients treated with anti-TNF agents [40]. Infliximab was reported to improve or stabilise RA-ILD in a total of 5 patients, but most case series described adverse effects. In large studies, respiratory complications were often the most common serious adverse events. Two large Japanese series of RA patients both associated adalimumab with progressive ILD, confirming earlier BSR reports. Etanercept was described as potentially improving outcome in case reports of two RA patients with ILD, but larger reviews reported deterioration or death in many RA-ILD patients. A report of nearly 14,000 RA patients on etanercept recorded ILD as one of the most frequent developments, and importantly it was later demonstrated that concomitant methotrexate therapy could reduce this risk.

To date there are 11 studies reporting pulmonary outcomes in patients with RA-ILD treated with rituximab, which include a total of 278 patients whose results can be adequately evaluated. In total, improvement was reported in 17%, stability in 76% and deterioration in 7% over a period of at least 12 months. The single largest study showed that rituximab halved the risk of functional impairment [41]. Data pooled from the three next largest studies demonstrated a significant reduction in mortality in RA-ILD patients over five years among those who received rituximab as their first biologic as compared to those initially treated with anti-TNF agents [42, 43, 44]. More details are shown in Table 2.

There are 7 studies describing the effect of abatacept on the lungs of patients with RA-ILD, comprising a total of 376 patients whose data is available for adequate assessment. Overall, improvement was described in 16%, stability in 72% and deterioration in 12% over a period of 12 months. The largest study came from a multi-centre Spanish cohort where results were consistent across both imaging and lung function indices and allowed significant steroid dose reductions [45]. An Italian multi-centre study showed comparable results [46]. One large cohort study demonstrated a 56% reduction in the incidence of exacerbation of ILD with abatacept compared to anti-TNF therapy [47]. More details are shown in Table 2.

There are 12 reports describing the pulmonary effects of tocilizumab in patients with RA-ILD, although 5 of these are single cases. A total of 88 patients had adequate data available to allow assessment. In total, improvement was noted in 16%, stability in 65% and deterioration in 19% over a period of twelve months or more. The largest and most detailed series comes from Italy, where improvement or stability in lung function was described in nearly 90% with radiological stability in over 80% [48]. A large retrospective case control group of 78 Japanese patients on tocilizumab related articular disease activity to adverse pulmonary outcome [49]. More details are shown in Table 2.

Overall, the data suggests that anti-TNF agents are probably best avoided in patients with RA-ILD. Enough evidence has now accumulated to justify the use of either rituximab or abatacept in RA-ILD patients [50], while the data on tocilizumab in this setting is presently limited but offers some reassurance. While such data are encouraging, we still need randomized controlled trial data to assess comparative efficacy and safety of a range of biologic therapies in RA-ILD.

Janus Kinase inhibitors have been a relatively recent introduction into the therapeutic armamentarium for RA. Tofacitinib inhibits both JAK1 and JAK3 pathways, while baricitinib blocks JAK1 and JAK2 signalling. Both drugs are licensed for use in RA but there are few data on their effect on RA-ILD. In one clinical development trial of RA patients involving both agents, 0.1% of the patients developed ILD, with low rates of ILD also reported in both pre- and post-marketing surveillance of tofacitinib. In open-label extensions, ILD developed in 27 out of 4,174 RA patients treated with JAK inhibitors, with one case for every 2,280 patient years of treatment [51]. Three deaths have been reported from progressive RA-ILD but tofacitinib was reported to stabilise lung function in a further 3 patients with RA-ILD [52]. It therefore appears that both these agents can justifiably be used to treat articular disease in patients with RA-ILD.

Role of corticosteroids

Oral corticosteroids have been used in the treatment of RA for 70 years but significant complications from their long-term use was identified within a decade. The advent of more effective therapeutic options may not yet have obviated their role in managing articular disease and associated fatigue, especially in the elderly. However, long term therapy [53] and higher doses of oral corticosteroids [54] are well known to be associated with increased risks of serious infection and a recent review of the management of RA-ILD in the elderly suggests such approaches are now best avoided in this group [55].

WHICH AGENTS CAN IMPROVE OUTCOME FOR RA-ILD PATIENTS WITH PROGRESSIVE LUNG DISEASE?

The role of specific drug therapy in the treatment of progressive ILD in RA patients has become a little clearer of late. The absence of prospective clinical studies has complicated the accumulation of interpretable data, but three groups of therapeutic agents have now emerged as having potential clinical value in the treatment of RA-ILD: biologics, immunosuppressive agents and anti-fibrotic agents.

Among the biologic agents, both rituximab and abatacept have been shown to improve physiologic parameters in 17% of RA-ILD patients, often with concomitant radiological improvement, over a period of at least 12 months. Each agent was also associated with a high percentage of stabilisation of the same parameters (76% and 72% respectively) [41, 45]. Mortality was significantly reduced among RA-ILD patients treated with either rituximab [42, 43] or abatacept [46, 47]. With both agents, there was a trend for greater effectiveness among patients with NSIP as opposed to UIP, but this was not significant. The data for efficacy with tocilizumab is more limited numerically, although improvement/stability has been reported in nearly 90% in one series [48].

Immunosuppressive drugs may play an important role in the management of progressive RA-ILD, but the evidence base for these has evolved considerably of late. The risks of oral steroids in idiopathic pulmonary fibrosis (IPF) were demonstrated a decade ago [56], although they continued to be used in the treatment of RA-ILD. No controlled trials of steroid have been conducted in RA-ILD, but evidence has slowly accumulated that their long-term use may be associated with overall greater mortality, often from infection [57]. Even when used in combination with other agents, steroids have rarely shown benefit over controls [58]. While short term steroid therapy to aid remission induction in NSIP may be justified, long term steroids should be avoided in RA-ILD and the use of steroids in UIP is actively discouraged.

Cyclophosphamide has been given to many RA-ILD patients, usually as an intravenous infusion in combination with methylprednisolone. No controlled clinical trials have been reported in RA-ILD, and it is usually reserved for rapidly progressive disease.

Mycophenolate has fewer side effects than cyclophosphamide but there are no prospective studies in RA-ILD. Several small retrospective studies reported benefit [60] and a large retrospective UK study reported improved survival with mycophenolate when compared to azathioprine [11]. It was suggested that efficacy may be greater in patients with NSIP than UIP and that the combination with rituximab may prove more effective. Calcineurin inhibitors such as cyclosporin and tacrolimus have been used in small numbers of RA-ILD patients, but insufficient consistent or meaningful data are available.

Anti-fibrotic agents have recently been shown to be effective in slowly the progression of fibrosis in IPF and nintedanib and pirfenidone are now both licensed for this indication. Each agent has been used in RA-ILD where they may benefit inflammatory as well as fibrotic components of the disease. Gastrointestinal side effects are common. Combining biologic or immunosuppressive therapy with an anti-fibrotic drug may further increase efficacy.

Nintedanib was reported to be efficacious in a patient with RA-ILD in 2018 [61]. It was subsequently compared to placebo in 89 RA-ILD patients in the INBUILD trial [62] where the annual rate of decline in vital capacity was reduced by 58% receiving active treatment. Most patients were smokers while 86% had UIP and did at least as well as those with less fibrotic radiological patterns. Pirfenidone was effective in slowing the rate of decline in vital capacity and gas transfer in a large multi-centre study of unclassifiable progressive fibrosing ILD over 6 months [63]. No formal reports of its use in RA-ILD have yet been published although the

TRAIL1 study is currently assessing the efficacy of pirfenidone in 270 patients with RA-ILD (TRAIL1) [64].

Further trials

Several trials of considerable relevance are either ongoing or planned to assess treatment paradigms in RA-ILD. These include the TRAIL1 study which will report on the efficacy of pirfenidone using mortality and lung function as endpoints and is hoped to demonstrate efficacy equivalent to that reported in IPF. The effect of abatacept on lung function over a twelve-month period is being assessed in greater detail in a study which is expected to confirm the encouraging results already reported from Italy and Spain. The potential effects of JAK inhibitors are presently being investigated in a comparison of tofacitinib against methotrexate, using HRCT as the major endpoint, while a further study comparing JAK inhibitors against mycophenolate is being discussed. These studies will not only inform clinicians whether JAK inhibition benefits patients with RA-ILD, but should also help to clarify the potential roles of both methotrexate and mycophenolate, neither of which have yet been previously tested in a prospective randomised study in this setting.

Other considerations

All patients with RA-ILD should be strongly advised to stop smoking. Pulmonary rehabilitation may improve dyspnoea and comorbidity assessed and treated. Vaccination against influenza should be offered annually and protection against pneumococcus should be administered every 5 to 10 years. During the COVID SARS-2 pandemic vaccination is strongly advised as severe COVID infection particularly involving the lung would be expected to produce very poor outcomes. Anticoagulation may play an important role in minimising the risk of pulmonary embolism. Lung transplantation should be considered in patients with no contra-indication. Oxygen should be offered to all patients disabled by hypoxia, many of whom will be in the terminal phase of their disease.

SUMMARY

This review offers readers insight into the current unmet needs in the diagnosis and management of ILD in patients with RA. It has highlighted the importance of developing an evidenced-based approach to the screening of RA patients for ILD, based on established risk factors. The importance of monitoring changes in lung function and structure has been highlighted and the need for a standard approach to this has been discussed. In addition, the present evidence-base to guide therapeutic intervention has been summarised and areas of ongoing need and future research identified. Over the next two years, it is anticipated that screening tools to identify RA patients at high-risk for ILD will be tested, validated and published. This will drive the need to agree both standard approaches to monitoring patients and thresholds for therapeutic intervention. Finally, within this time period we expect to have further and more robust therapeutic trial data to clarify and confirm the remaining questions about which agents to use and in which specific clinical settings.

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TABLE 1

To show risk factors for rheumatoid arthritis-associated interstitial lung disease

RA : rheumatoid arthritis; RA-ILD: rheumatoid arthritis-associated interstitial lung disease; ACPA: anti-citrullinated protein antibodies; RF: rheumatoid factor.

	Risk factors	References
Individual risk factors	• Male sex • Older age at RA onset • Obesity • Cigarette smoking • Carriers of the *MUC5B* rs 35705950 risk allele	1, 2, 3, 4, 5, 6, 7
RA-related risk factors	• Active RA • ACPA and/or RF positive status (?) high titre, specific subtypes of ACPA (?)	2, 5, 6, 8, 13, 14, 15, 16, 18
Biomarkers of interest in interstitial lung diseases not specific of RA-ILD	• CA-125 • MMP-7 • SP-D • KL-6	22, 26, 27

TABLE 2

To show the number of RA-ILD patients who have received different biologic therapies and the numbers (percentages) of patients who have demonstrated improvement, stability or deterioration over a period of at least 12 months. Improvement is defined as 10% or more increase in vital capacity (VC) or gas transfer (TLco), stability as change of less than 10% in VC or TLco, and deterioration as 10% or more decrease in VC or TLco.

BIOLOGIC	NUMBER	IMPROVEMENT	STABILITY	DETERIORATION	FIRST AUTHOR (number of patients)
RITUXIMAB	278	47 (16.9%)	211 (75.9%)	20 (7.2%)	F-D (68) Yusof (56) Druce (43) Kelly (37) Bacaura (19) Duarte (16) Fui (14) Chartrand (12) Mateson (10) Keir (2) Hartung (1)
ABATACEPT	376	60 (15.9%)	271 (72.2%)	45 (12.0%)	F-D (163) F-D (63) Mochi (55) Cassone (44) M-V (23) Nakashika (16) Kurata (12)
TOCILIZUMAB	88	14 (15.9%)	57 (64.7%)	17 (19.3%)	Manfredi (25) Otsuji (22) F-D (12) Nakashira (9) Kurata (7) Manfredi (4) M-V (4) Diamanti, F-D, Dobson, Keidel, Kawashiri Nohr (1)

The patients receiving all three therapies had roughly comparable mean baseline pulmonary function and radiological indices.

Figure 1. Unmet needs in screening for RA-ILD

Figure 2. Current knowledge in screening for RA-ILD

Figure 3. Proposal strategy for RA-ILD screening