Management of Rheumatoid Arthritis Patients with Interstitial Lung Disease: Safety of Biological Antirheumatic Drugs and Assessment of Pulmonary Fibrosis

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ABSTRACT: Interstitial lung disease (ILD) is one of the major causes of morbidity and mortality of patients with rheumatoid arthritis (RA). Accompanying the increased number of reports on the development or exacerbation of ILD in RA patients following therapy with biological disease-modifying antirheumatic drugs (DMARDs), RA-associated ILD (RA-ILD) has aroused renewed interest. Although such cases have been reported mainly in association with the use of tumor necrosis factor inhibitors, the use of other biological DMARDs has also become a matter of concern. Nevertheless, it is difficult to establish a causative relationship between the use of biological DMARDs and either the development or exacerbation of ILD. Such pulmonary complications may occur in the natural course of RA regardless of the use of biological DMARDs. Since rheumatologists currently aim to achieve remission in RA patients, the administration of biological DMARDs is increasing, even for those with RA-ILD. However, there are no reliable, evidence-based guidelines for deciding whether biological DMARDs can be safely introduced and continued in RA-ILD patients. A standardized staging system for pulmonary conditions of RA-ILD patients is needed when making therapeutic decisions at baseline and monitoring during biological DMARD therapy. Based on the available information regarding the safety of biological DMARDs and the predictive factors for a worse prognosis, this review discusses candidate parameters for risk evaluation of ILD in RA patients who are scheduled to receive biological antirheumatic therapy.

KEYWORDS: interstitial lung disease, rheumatoid arthritis, biological antirheumatic drugs, pulmonary fibrosis, acute exacerbation

Introduction

Although rheumatoid arthritis (RA) is considered an autoimmune inflammatory disease in which persistent inflammatory changes occur predominantly in the synovial joints, ~40% of patients suffer from some type of extraarticular manifestations at some time during the course of their disease.[1–3] The presence of extraarticular manifestations is associated with poor survival in RA patients.[4–7] The respiratory system is one of the most frequent targets of extraarticular manifestations and includes rheumatoid nodules, pleural complications, airway disease, and interstitial lung disease (ILD).[8–10] The data reported for the prevalence and incidence of ILD in RA patients vary depending on the criteria used to define the disease, the sensitivity of clinical examinations employed, and the patient populations examined. Recent studies showed that the prevalence of clinically significant ILD was 7.7%–12% of RA patients.[11–15] Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the main histological and radiological patterns of ILD in RA patients.[11,16–20] There are a number of studies showing that the presence of ILD is apparently associated with shortened survival of RA patients.[12,14,21–25]

RA-associated ILD (RA-ILD) has attracted renewed interest because of the increased number of reports on adverse reactions of the lung during biological disease-modifying antirheumatic drugs (DMARDs). Although it is difficult to establish a causal relationship, growing evidence highlights an association of the use of biological DMARDs with either the development of ILD or the exacerbation of preexisting ILD.[26–28] In daily practice, we often encounter RA-ILD patients whose articular disease activity is not controlled despite the use of nonbiological DMARDs. However, there are no evidence-based guidelines regarding the safety of introducing biological DMARDs in such patients.

Here, recent medical literature is reviewed regarding the development of ILD or the exacerbation of preexisting ILD in RA patients receiving biological DMARDs. The necessity of a standardized staging system for pulmonary conditions of RA-ILD patients prior to and after the commencement of biological DMARD therapy is also discussed.

Pharmaceutical Therapy for RA

DMARDs are currently categorized as either biological DMARDs or synthetic DMARDs. Biological DMARDs were designed to target specific molecules and pathways in the immune system. Five tumor necrosis factor-α (TNFα) inhibitors (infliximab: a chimeric anti-TNFα monoclonal antibody; etanercept: a soluble TNF receptor; adalimumab and golimumab: humanized anti-TNFα monoclonal antibodies; certolizumab pegol: an antigen-binding fragment of humanized anti-TNFα monoclonal antibody conjugated to polyethylene glycol), a humanized anti-IL-6 receptor monoclonal antibody (tocilizumab), a T-cell signaling inhibitor (abatacept), and a chimeric anti-CD20 monoclonal antibody (rituximab) are mainly used in biological DMARD therapy for RA. Synthetic DMARDs include conventional compounds, such as methotrexate (MTX), sulfasalazine, leflunomide, and hydroxychloroquine, and targeted synthetic DMARDs, such as tofacitinib, a novel synthetic DMARD designed to target Janus kinases.[29]

The early use of MTX as the first-line DMARD coupled with the popularity of biological DMARDs has changed the course of RA and improved patient outcomes and quality of life. The combined use of biological DMARDs and MTX has produced a significant improvement in clinical, radiological, and functional outcomes.[30–34] Currently, the therapeutic goals are to induce remission, but this has introduced a dilemma when making therapeutic decisions for RA-ILD patients. We should carefully weigh the risks and benefits before denying the use of biological DMARDs to such patients.

Development or Exacerbation of ILD in RA Patients Receiving TNFα Inhibitors

Case reports. There are a considerable number of cases reported on the new onset or exacerbation of RA-ILD during treatment with TNFα inhibitors, including infliximab, etanercept, and adalimumab.[35–57] Ostor et al first reported four fatal cases in which previously asymptomatic ILD suddenly and rapidly caused respiratory failure after the second or third infusion (3–10 weeks) of infliximab for RA. These patients had concomitantly received synthetic DMARDs such as azathioprine or leflunomide, instead of MTX.[40,42] Another case showed that an acute progression of preexisting ILD had occurred only one week after the first infusion of infliximab together with leflunomide. Despite intensive therapy, the patient died two weeks after admission.[47] These reports caused concern regarding the safety of TNFα inhibitors when treating RA-ILD patients. In addition, two fatal

cases were reported in association with etanercept therapy, in which acute progression of preexisting ILD occurred: one RA patient had received etanercept for six weeks (12 injections) in combination with MTX,[43] and the other was treated with etanercept and salazosulfapyridine for eight weeks.[53] A fatal outcome was also reported in two RA patients without preexisting ILD. These patients had received infliximab for 10 weeks (three infusions) and adalimumab for 10 weeks, in combination with MTX, respectively.[38,45] Dascalu et al reported one case in which a causative relationship was clearly established between acute ILD and adalimumab therapy. After 3.5 years of adalimumab therapy for RA, the patient, who had no preexisting lung disease, developed acute ILD, but her clinical status improved following steroid therapy and discontinuation of adalimumab. The patient was rechallenged with adalimumab because of severe RA flare, and three weeks later, ILD recurred. Consolidation and ground-glass attenuation appeared in the same areas as before. Adalimumab was stopped, with improvement of symptoms. These findings were consistent with recurrent drug-induced lung injury.[49]

Koo et al reviewed the medical records of RA-ILD patients who had received treatment with TNFα inhibitors at the authors' institution. Among 24 patients identified, six (25%) died of the following conditions: diffuse alveolar hemorrhage (two cases), acute deterioration of ILD (two cases), pneumonia (one case), and septic shock following septic arthritis (one case). An acute deterioration of ILD occurred within three months of etanercept therapy.[58]

Several studies showed an association of the use of new TNFα inhibitors (golimumab and certolizumab pegol) with the development or the exacerbation of ILD in RA patients.[26,59–62] One patient died from respiratory failure caused by an acute deterioration of preexisting ILD three months after commencing certolizumab in combination with leflunomide.[60] Three patients without evidence of preexisting ILD developed severe ILD one–three months after starting treatment with certolizumab alone or in combination with MTX. Among these patients, one eventually died from respiratory failure and the other two developed impaired lung function that required the use of a home oxygen on exertion.[59,61,62]

Postmarketing surveillance reports. Postmarketing surveillance reports by pharmaceutical companies in Japan indicated a high incidence of ILD in RA patients receiving infliximab (0.5% of 5000 patients), etanercept (0.6% of 7091 patients), and adalimumab (0.6% of 3000 patients). There was no significant difference in the incidence rates of ILD among the three TNFα inhibitors. The incidence rates are relatively low but are not negligible.[63–65]

Observational studies. Using data in the National Data Bank for Rheumatic Diseases, Wolfe et al showed that the incidence of hospitalization for ILD was 260 per 100,000 patient-years, and among those hospitalized for ILD, 27% died. Preexisting lung problems were identified in 67% of patients. But only one case in the 100 hospitalizations that

were examined in greater detail suggested a temporal association of ILD with the exposure to DMARDs. In addition, associations were confounded by therapeutic use of DMARDs for preexisting ILD. The authors concluded that there was no evidence of an association between infliximab therapy and hospitalization for ILD.[66] In fact, there are several cases reported in which TNFα inhibitors, such as infliximab and etanercept, improved clinical symptoms and signs and stabilized pulmonary function in RA-ILD patients.[67–70]

Through an examination of data from 8417 patients with autoimmune diseases who were members of Kaiser Permanente Northern California, Herrinton et al showed that the use of TNFα inhibitors did not increase the development of ILD compared with synthetic DMARDs. Since this study excluded patients with preexisting ILD, however, there is no information on whether TNFα inhibitors exacerbate preexisting ILD.[71]

Using data from the British Society for Rheumatology Biologics Register, Dixon et al identified 367 patients with preexisting RA-ILD and compared mortality rates between patients treated with TNFα inhibitors and those receiving synthetic DMARDs alone. Seventy of 299 patients (23%) in the TNFα inhibitor group died, while 14 of 68 (21%) in the synthetic DMARD group died. The mortality rate was 68 deaths per 1000 patient-years for the former group and 92 per 100 patient-years in the latter group. RA-ILD was an underlying cause of death in 21% of patients in the TNFα inhibitor group and 7% in the synthetic DMARD group. Despite an initial concern about the safety of TNFα inhibitors in patients with RA-ILD, the mortality rate did not increase following the treatment with TNFα inhibitors compared with synthetic DMARDs, but the proportion of deaths attributed to RA-ILD is higher in the TNFα inhibitor group. These results may reflect the possibility that physicians in the UK are currently making appropriate decisions regarding eligibility when considering the use of TNFα inhibitors in the treatment of RA-ILD patients. The authors emphasized that physicians should not assume that it is safe to prescribe TNFα inhibitors to unselected patients with RA-ILD.[72]

Systemic literature review. Through the Medline search of reported cases of the onset or exacerbation of ILD during treatment with biological DMARDs, Perez-Alvarez et al showed the following: 38% of the cases had ILD when DMARDs were introduced; biological DMARDS used at the time of the development or exacerbation of ILD were overwhelmingly TNFα inhibitors (97% of all cases of ILD); ILD appeared within a mean of 26 weeks after initiation of biological DMARDs; and the overall mortality rate was one-third, rising to two-thirds in patients with preexisting ILD.[27] Another systemic literature review showed the following: there was a general impression of increased pulmonary toxicity during treatment with biological DMARDs, especially TNFα inhibitors, alone or in combination with MTX; for TNFα inhibitors, MTX, or leflunomide, the estimated prevalence

of possibly induced ILD was ~1%; most cases occurred within the first 20 weeks after the initiation of the therapy; and this pulmonary complication was rare but could be fatal.[28]

Development or Exacerbation of ILD in RA Patients Receiving Biological DMARDs other than TNFα Inhibitors

Little information is currently available regarding the safety of biological DMARDs other than TNFα inhibitors, including tocilizumab, abatacept, and rituximab, in RA-ILD patients. Several cases reported in the literature provide detailed data regarding the development or exacerbation of ILD during treatment with such biological DMARDs.[73–78]

Concerning tocilizumab therapy, one fatal case was reported, in which preexisting RA-associated UIP was rapidly exacerbated 10 months after the introduction of tocilizumab monotherapy. This case was complicated by emphysema.[74] Another case also showed an acute worsening of preexisting RA-associated pulmonary fibrosis and emphysema after two-year tocilizumab monotherapy. Fortunately, clinical symptoms and pulmonary function were markedly improved with steroid therapy.[75] In one case showing a clear temporal relationship, an RA patient developed organizing pneumonia three days after the first infusion of tocilizumab. MTX had been used for two years, but no pulmonary symptoms or signs had been reported during this period.[73] In contrast, Mohr and Jacobi reported an RA patient who had developed ILD during MTX therapy. Despite a withdrawal of MTX, pulmonary symptoms worsened, but the patient markedly improved within 16 weeks of tocilizumab monotherapy. The findings suggested that tocilizumab may represent a therapeutic option for RA patients with rapidly progressing ILD.[79] Therapeutic potential was also reported in a patient with refractory, undifferentiated autoimmune inflammatory disease. The patient developed a systemic inflammatory condition that included desquamating ILD. An IL-1 receptor antagonist, anakinra, rapidly improved the patient's inflammatory symptoms, but there was no improvement in the lung disease. ILD in this case responded well to tocilizumab therapy.[80]

Postmarketing surveillance reports by pharmaceutical companies in Japan indicated an incidence of ILD in RA patients receiving tocilizumab (23 out of 3881 patients; 1.28 per 100 patient-years). Among these 23 cases, 13 had concurrent or a medical history of ILD.

Through an examination of pooled data from eight clinical trials of intravenous abatacept therapy for RA, Weinblatt et al showed that ILD occurred in 11 out of 3171 patients (0.3%), and the incidence rate was calculated to be 0.11 per 100 patient-years. During the pooled short-term period, the incidence rate was 0.09. No ILD-related event was reported in the placebo control group. The authors concluded that the incidence of ILD was low, with no apparent increase in risk over time.[81] In this study, however, it was unclear whether abatacept is safe for RA patients with preexisting ILD. Only

one case report in the literature describes an abatacept-related exacerbation of preexisting ILD. In this case, the patient was registered in the Phase III trial of abatacept in Japan, but two days after the administration of abatacept, frothy sputum frequently appeared. Interstitial shadows had worsened on computed tomography (CT) scans taken on day 13 of the trial, and the patient withdrew from the trial.[78]

Although rituximab had a high incidence of pulmonary toxicity in patients with lymphoma, only a few cases were reported involving inflammatory rheumatic diseases.[26] It is of note that several studies supported the idea that rituximab may be an effective, potentially life-saving, therapeutic intervention in the treatment of RA-ILD.[82–84] Matteson et al conducted a 48-week, open-labeled, pilot study for 10 patients with progressive RA-ILD. Although there were significant adverse events, including two fatal cases, pulmonary function and radiological findings remained stable in the majority of study completers.[84] Keir et al performed a retrospective assessment of 50 patients with severe and progressive ILD of various etiologies, excluding idiopathic pulmonary fibrosis (IPF), who had received rituximab as rescue therapy because of unresponsiveness to conventional immunosuppressants. Among these ILD cases, 33 were associated with inflammatory rheumatic diseases. Although 10 patients died from the progression of ILD, %predicted for forced vital capacity (%FVC) was improved and %predicted for diffusing capacity for carbon monoxide (%DLco) was stable following 6–12 months of rituximab therapy.[83] In the future, controlled trial studies with large sample sizes would be required in order to establish the therapeutic role of rituximab in the management of intractable RA-ILD.

Uncertainty of a Causative Relationship Between the use of Biological DMARDs and Either the Development or Exacerbation of ILD

The reports mentioned above have raised concerns regarding the safety of biological DMARDs. Clinicians should remain vigilant for the development of ILD and the exacerbation of preexisting ILD, which are relatively rare but can be fatal, when considering biological DMARD therapy for RA patients. Nevertheless, it seems difficult to establish a definite causative relationship between the use of DMARDs and such adverse events. Therefore, it remains unclear whether the new onset of ILD and the exacerbation of preexisting ILD seen during DMARD therapy reflect pulmonary toxicity induced by the drugs or whether these events occur merely as one of the extraarticular manifestations in the natural course of RA regardless of the use of biological DMARDs. There are only a few cases reported in which a causative relationship between biological DMARDs and ILD was clearly established. In addition, although some cases of DMARD-related ILD represent examples of the direct toxicity of drugs, this pulmonary complication may also be due to modification of inflammatory processes of RA in the lung through a drug-induced imbalance of the immune system.

Predictive Factors for Poor Prognosis in IPF Patients

Through the collaborative efforts of the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association, international evidence-based guidelines for the diagnosis and management of IPF have been developed. Based on the best available evidence, the guidelines have listed factors associated with an increased risk of mortality in IPF, including male gender, advanced age, level of dyspnea, DLco <40% predicted, high-resolution computed tomography (HRCT) features (extent of fibrosis and honeycombing), pulmonary hypertension, and desaturation ≤88% during the six-minute walk test as baseline factors as well as an increase in level of dyspnea, a decrease in FVC by ≥10% in absolute value, a decreases in DLco by ≥15% in absolute value, and worsening of fibrosis on HRCT as longitudinal factors.[85]

Baseline DLco is a reliable predictor, and a threshold of 40% predicted is associated with an increased risk of mortality in IPF patients.[86–90] A baseline FVC is of unclear predictive value for early death when used alone, but it seems to be informative when used in combination with other parameters. Ley et al showed that a staging system using age, gender, and baseline predictive values of DLco and FVC is effective in predicting mortality.[91] Longitudinal changes in physiology seem to have more important values as the predictor of mortality. A decline of DLco (a decrease of ≥15% in absolute value over 6–12 months) is associated with decreased survival.[88,92–94] A decline of FVC over 6–12 months is also significantly associated with decreased survival, and a 10% change in absolute value is predictive of mortality.[92–98] Zappala et al showed that a marginal decline in FVC (a decrease by 5% to 10%) at six months also denotes a poor outcome.[99] Another study reported that a decline >10% in FVC at six months is a significant risk factor for acute exacerbation (AE) at early stages.[100] These variables are commonly measured in routine practice. Besides changes in FVC and DLco, a decline in alveolar–arterial oxygen difference ($AaPo_2$) of ≥5 mmHg over 6–12 months was reported as a predictive factor for survival.[92,94] Changes in partial pressure arterial oxygen (PaO_2) and oxygen saturation over 6–12 months are also predictive of survival time.[94]

Although there is still room for improvement in terms of reproducibility, the six-minute walk test is a widely used clinical tool. Desaturation during this test, defined as a fall in percutaneous oxygen saturation (SpO_2) to ≤88% seems to be associated with a high mortality in IPF patients.[101,102] Shorter walk distance is also a prognostic factor in IPF.[102–106] The Japanese Respiratory Society Guidelines classified the disease severity staging of IPF into the following four stages based on PaO_2 at rest and lowest SpO_2 during the six-minute walk (Table 1). Recently, Homma et al showed that this severity classification system is highly correlated with AE (incidence and time to onset), baseline predicted values of vital capacity (VC) and DLco, and survival rate in IPF patients.[107]

Patients with a typical UIP pattern on HRCT experience the highest mortality among those with other types of idiopathic ILD.[108] A CT-based grading of extent of pulmonary fibrosis has a predictive value for disease progression and mortality in patients with IPF and in those with fibrosing alveolitis associated with systemic sclerosis.[109] The extent of fibrosis on CT can be calculated using physiologic compositions, including percent predicted FVC, DLco, and forced expiratory volume in one second (FEV_1). This index is a more accurate prognostic determinant in UIP than is an individual physiologic parameter.[93,110]

Prognostic Factors in RA Patients with ILD

Similar to idiopathic ILD, the UIP pattern is associated with a worse prognosis in RA patients, compared with the NSIP pattern.[17,18,20,111–114] Several studies showed that RA patients with the UIP pattern have significantly better survival rates than IPF patients do.[115–118] Recently, Goh et al proposed a severity staging system for systemic sclerosis-associated ILD based on a combined evaluation with HRCT and a pulmonary function test (PFT). In this system, the optimal threshold of the extent of disease on HRCT was 20% in order to classify patients as having extensive ILD or limited ILD. An FVC threshold of 70% was used for patients whose disease extent was not determined in the HRCT grading. This staging system was strongly predictive of mortality.[119] Using the same HRCT-based grading system for disease extent, Sathi et al showed that patients with limited RA-ILD have a good prognosis, but those with extensive disease have a poor prognosis.[120] In the recent and also the largest study for RA-ILD in the UK, Kelly et al showed that the presence of UIP and extensive disease, defined as a disease extent of 20% or more on HRCT, was associated with increased mortality.[20]

Besides the pattern and extent of fibrosis, several variables (older age, male gender, low socioeconomic status, high disease activity, low FVC and DLco at baseline, and declined DLco) have been reported in association with mortality in RA-ILD.[24,111,114,117,118,121,122]

Recently, Cottin et al showed that combined pulmonary fibrosis and emphysema (CPFE) should be recognized as a novel, distinct pulmonary manifestation within the spectrum of lung diseases associated with inflammatory rheumatic diseases in smokers or former smokers, especially RA and systemic sclerosis.[123] Several studies suggested that the complications of emphysema with IPF are associated with a high prevalence of pulmonary hypertension and poor prognosis.[124,125] Further studies are required to determine whether the same may be true of RA patients.

AE, which has been recognized as a relatively common and highly lethal clinical event occurring in patients with underlying IPF, also occurs in RA-ILD patients. Through retrospective analysis, Park et al reported that AE occurred in four out of 93 patients with ILD associated with inflammatory rheumatic diseases (annual incidence rate, 3.3%). Three out of the four were RA-associated UIP patients and all died.[126] Suda et al also reported that among 83 patients with ILD associated with inflammatory rheumatic diseases (including 25 RA patients), five RA patients developed this complication. The one-year incidence was 2.6% in RA-ILD patients, and four patients died.[127] In a retrospective case–control study, Hozumi et al showed that 20% of 51 RA-ILD patients developed AE (annual incidence rate, 2.8%), and 64% died of initial AE. Advanced age, the use of MTX, and the presence of UIP were the risk factors for the development of AE.[128] Although these are small, retrospective studies, they all collectively raise a concern that AE has a serious impact on the survival of RA-ILD patients. However, it is unclear whether AE is a manifestation of a pulmonary condition due to an unidentified cause or whether it represents an inherent acceleration of the pathological process in the course of ILD.

Management of RA Patients with ILD

Since rheumatologists currently aim to achieve remission in RA patients, the use of biological DMARDs is often considered, even for those with RA-ILD. The extent of the disease and the severity of functional impairment of RA-ILD patients vary at the time of diagnosis. We therefore need to fully assess pulmonary physiology prior to biological DMARD therapy using a reliable and standardized evaluation system. Based on the baseline data, we need to carefully provide RA-ILD patients with evidence-based information regarding the risks and benefits of biological DMARDs. As mentioned above, a number of studies have identified predictive factors for survival in RA-ILD patients; however, the accuracy may be hampered by the retrospective nature of most studies and variations in the study design. At present, the extrapolation of findings in IPF to the management of RA-ILD may be justified, given that UIP is a more common histological and radiological pattern in RA-ILD.[16–18,20] Based on the findings regarding predictive factors for a worse prognosis so far reported in IPF patients and RA-ILD patients, candidate parameters are proposed for risk evaluation, at baseline and during follow-up periods, of pulmonary conditions in RA patients who are scheduled to receive biological DMARDs (Table 2). A disease extent

Table 1. Disease severity staging of IPF according to the Japanese Respiratory Society Guidelines.

STAGE	PaO_2 AT REST	SpO_2 DURING SIX-MINUTE WALK TEST
I	≥80 Torr	-
II	≥70 Torr and <80 Torr	If <90%, classified as stage III
III	≥60 Torr and <70 Torr	If <90%, classified as stage IV
IV	<60 Torr	-

Abbreviations: IPF, idiopathic pulmonary fibrosis; PaO_2, partial pressure arterial oxygen; SpO_2, oxygen saturation as measured using pulse oximeter.

of >20% and the UIP pattern on HRCT, a baseline DLco <40% of predicted, and stages III and IV based on PaO_2 at rest and desaturation after the six-minute walk test are currently used at our hospital as risk-evaluation parameters when deciding whether or not to introduce biological DMARDs. These parameters have been identified mainly in IPF patients, but not in studies for RA-ILD patients who were treated with biological DMARDs. Currently, there are no prognostic factors identified in prospective studies for RA-ILD patients receiving biological DMARDs. Thus, this risk evaluation is made on the assumption that RA patients with higher risks for a worse prognosis of ILD in the natural course would also have a higher probability of developing DMARD-induced exacerbation of underlying ILD during this therapy. Nevertheless, these parameters will provide important information regarding the extent and severity of RA-ILD at baseline and its progression during biological DMARD therapy.

The six-minute walk test may not be feasible for RA patients because articular disease may restrict mobility. However, this test can be performed safely and quickly in an outpatient clinic setting. In addition, biological DMARD therapy is currently considered for use on patients with early-stage RA, whose activities of daily living are relatively maintained. Since desaturation with exercise (SpO_2 <90%) is an important parameter for severity of ILD, we routinely perform this test, or its equivalent, on RA patients who are scheduled for biological therapy. If patients are incapable of walking, we ask for other types of motion such as repeatedly standing up and sitting down or repeatedly raising their hands.

The progression of ILD, regardless of it being the result of the natural disease course or accelerated by biological DMARD, may be heralded by the onset or worsening of dyspnea. However, dyspnea is a subjective complaint. Some patients, such as those of advanced age and those with chronic pulmonary disease, are inclined not to complain of dyspnea.

We should advise RA patients to visit a doctor immediately if they note any unusual physical conditions. SpO_2 at rest and after the six-minute walk should be measured by pulse oximeter during each visit, regardless of their symptoms and risk levels for poor outcomes at baseline. Although certain factors and conditions may influence the results, pulse oximetry is a simple, rapid, and noninvasive method of measuring oxygen saturation in the blood. Pulmonary physiology should be monitored over periods of three–six months using a PFT. Changes from baseline in absolute values of DLco and FVC (decrease by ≥15% and 10% in absolute values over six–12 months, respectively) are associated with decreased survival. But the optimal time intervals for repetition of FVC and DLco measurements have not yet been determined. Earlier repetition is required for patients who have clinical features suggestive of a more rapidly progressive course or who are categorized at baseline into the high-risk group for early death. For patients experiencing declines of the physiologic parameters, worsening of fibrosis from baseline should be evaluated using HRCT.

It is difficult to determine whether the exacerbation of ILD seen during biological DMARD therapy is modified and accelerated by DMARDs (including biological and synthetic DMARDs used concomitantly) or whether it merely reflects a progression in the natural course of RA. Rheumatologists should consult with expert pneumologists and radiologists in ILD to determine a possible cause of the exacerbation of pulmonary conditions. For patients with worsening pulmonary physiology, a decision on whether or not to discontinue drugs should be made on a case-by-case basis with a careful consideration of the risks and benefits. In addition, the possibility of alternative diseases that present as an acute respiratory worsening during biological DMARD therapy (serious infections, pulmonary embolus, congestive heart failure, pneumothorax, malignancy, sarcoidosis, etc) should be considered. In particular, *Pneumocystis jirovecii* pneumonia should be included in the differential diagnosis of acute-onset diffuse interstitial pneumonia in RA patients receiving immunosuppressive therapy.[129] In suspected cases, discontinuation of all drugs and prompt evaluation for a differential diagnosis should be undertaken.[85]

Conclusions

ILD is a common extraarticular manifestation of RA, which is apparently associated with morbidity and mortality in affected patients. Biological DMARDs have substantially improved the quality of life of RA patients. Since the therapeutic goal has become remission, their use for this patient population will increase. But a number of reports have raised clinicians' concern regarding the use of biological DMARDs for RA-ILD patients. A baseline assessment of the severity and extent of ILD using objective pulmonary parameters is required for therapeutic decisions related to whether biological DMARDs should be used. Careful counseling and patients' consent regarding the risks and benefits are mandatory. Regular monitoring of pulmonary conditions is also needed during

Table 2. Candidate parameters for risk evaluation at baseline and during follow-up periods for RA-ILD patients who are scheduled for biological DMARD therapy.

PARAMETERS	HIGH RISK FOR POOR OUTCOMES
Baseline	
HRCT pattern	UIP pattern
Severity stage	III and IV
DLco,% predicted	<40% predicted
Extent on HRCT	>20%
Follow-up period	
SpO$_2$ after six-minute walk or equivalent	<90%,
Decrease in FVC	≥10% in absolute value
Decrease in DLco	≥15% in absolute value

biological DMARD therapy. Unfortunately, it is not clear whether the exacerbation of ILD is due to the acceleration by biological DMARDs or whether it reflects simply the progress in the natural course. Interdisciplinary efforts between rheumatologists, radiologists, and pulmonologists are critical for RA-ILD patients to receive benefits from the introduction and continuation of biological DMARDs. This review suggests that predictive factors for poor outcomes were driven mainly by the extrapolation of the findings in IPF, on the premise that patients with a poor prognosis in the natural course of RA-ILD would also have a poor prognosis for biological DMARD-related ILD. Large-scale, multicenter, prospective, longitudinal cohort studies are required to evaluate the impacts of biological DMARDs on the lung, which should include parameters for RA disease activity, oxygen saturation at rest and after exercise, lung physiology (FVC and DLco), and HRCT at baseline and during follow-up periods. Such studies will lead to a better understanding of predictive factors for poor outcomes in RA-ILD patients who are receiving biological DMARD therapy.

Author Contributions

Conceived the concept and design: SM. Wrote the first draft of the manuscript: SM. Contributed to the writing of the manuscript: SM. Agrees with manuscript results and conclusions: SM. Developed the structure and arguments for the paper: SM. Made critical revisions and approved final version: SM. The author reviewed and approved of the final manuscript.

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