Practical Management of Respiratory Comorbidities in Patients with Rheumatoid Arthritis

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Received: June 5, 2017 / Published online: August 14, 2017 © The Author(s) 2017. This article is an open access publication

ABSTRACT

Lung disease is one of the most common causes of extra-articular morbidity and mortality in patients with rheumatoid arthritis (RA). Development of pulmonary manifestations may be due to the systemic disease itself; to serious respiratory adverse events such as pneumonitis and infections secondary to therapy; or to lifestyle habits such as smoking. Rheumatologists often need to make important treatment decisions and plan future care in RA patients with respiratory comorbidities, despite the absence of clear evidence or consensus. In this review we evaluate the clinical assessment and management of RA-associated interstitial lung disease, bronchiectasis, serious (including opportunistic) infection, and smoking-related diseases. We summarize the international recommendations where available, refer to published best practice on the basis of scientific literature, and propose practical management suggestions to aid informed decision-making.

Keywords: Disease-modifying antirheumatic drugs; Respiratory tract diseases; Rheumatoid arthritis; Safety; Smoking

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disorder. Although the predominant clinical feature of RA is inflammation of the synovial lining of joints, RA has numerous extra-articular manifestations. Lung disease is a major contributor to the extra-articular morbidity and mortality of RA [1]. Pulmonary manifestations of RA include RA-related interstitial lung disease (RA-ILD), bronchiectasis (BR), respiratory tract infections (RTI), pleural disease and, rarely, vascular disease [2]. In addition, because there is an increased prevalence of smoking in patients with RA [3], RA is associated with an increased incidence of lung cancer compared to the general population [4].

Over the last 15–20 years the management of RA has been transformed with an ongoing expansion in the armamentarium of treatments available. Treat-to-target guidelines advocate early treatment, with the aim of achieving and
sustaining low disease activity (LDA) or remission [5, 6]. Therefore, most patients with RA are likely to be treated with conventional synthetic and/or biologic disease-modifying antirheumatic drugs (csDMARDs; bDMARDs) early and throughout the course of their disease. Clinicians now commonly encounter RA patients with both uncontrolled articular disease and respiratory comorbidity in whom informed decisions about the benefits and risks of different potential treatments have to be made. In this narrative review, we focus on and summarize the evidence for best practice in the real-world management of the major respiratory comorbidities of RA: RA-ILD, BR, infection risk, and smoking-related airways disease; and management of the joint manifestations of RA in the context of respiratory comorbidity.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

PREVALENCE OF SMOKING IN RA POPULATIONS AND RISKS OF SMOKING IN THE GENERAL POPULATION

Cigarette smoking is a risk factor for the development of RA. In a meta-analysis of 16 observational studies, the summary odds ratio (OR) for developing RA for 20 or more pack-years of smoking (vs. never smoking) was 2.31 (1.55–3.41) in men and 1.75 (1.52–2.02) in women [3]. The association is strongest for rheumatoid factor (RF)-positive RA. In the same meta-analysis, the summary ORs for RF-positive RA for men for ever, current, and past smokers (vs. never smokers) were 3.02 (2.35–3.88), 3.91 (2.78–5.50), and 2.46 (1.74–3.47), respectively [3]. This risk is thought to be related to gene–environment interaction. It is hypothesized that smoking leads to citrullination of proteins within the lung. In patients with one or more copies of the shared epitope (SE) this may be followed by the development of autoantibodies directed against citrullinated proteins (ACPA). Following exposure to a second trigger, subjects with the SE who are ACPA positive may then develop RA [7].

Since the majority of smokers with recent onset RA do not stop smoking [8], there is a higher prevalence of smoking in RA populations than in the general population. In a meta-analysis of four case–control studies involving 1415 RA patients and 1749 controls, Boyer et al. reported that the prevalence of smoking was approximately 50% higher in patients with established RA than in their matched controls from the general population (summary OR 1.56; 95% CI 1.35, 1.80) [9]. Between 21% and 33% of individuals with RA are current smokers and 50–75% are past smokers [8, 10–12].

In the general population, cigarette smoking is known to increase the risk of death from lung cancer, and chronic obstructive pulmonary disease (COPD) [13]. The risk rises with the duration of smoking and the number of cigarettes smoked per day. Strong inverse relationships are observed between the years since quitting smoking and deaths from lung cancer and COPD [13]. A systematic review of the literature up to 2007 concluded that, even in severe COPD, smoking cessation slows the rate of lung function decline and improves survival compared with continued smoking [14].

Smoking is also a strong risk factor for both sporadic idiopathic pulmonary fibrosis (IPF) and familial pulmonary fibrosis in the general population [15].

INTERSTITIAL LUNG DISEASE AND BRONCHIECTASIS

Epidemiology

RA-ILD is one of the most common respiratory comorbidities in RA and is associated with more severe RA [16]. Prevalence estimates vary between 10% and 30% [17, 18] depending on the population studied and the imaging modality used for detection. Patients with RA-ILD have a more than threefold increased risk of premature death [19, 20] compared to RA patients without ILD, and have a median survival of 3 years following diagnosis [19]. Whilst
RA is typically more common in women, RA-ILD is more frequent in men, with a ratio of 2:1 [21].

The association of RA with bronchiectasis (BR) has been recognized for many years. The prevalence of BR in RA has been estimated between 2% and 12% [22]. However, prevalence of up to 30% has been reported in studies using high-resolution computer tomography (HRCT) of the chest [22]. The coexistence of RA and BR is associated with higher mortality than BR alone [23].

**Predictors/Risk Factors**

Older age and male gender have been shown to be risk factors for RA-ILD in a number of studies [24, 25]. Important clinical risk factors include markers of RA severity such as high levels of RF [24, 26], ACPA positivity [27, 28], subcutaneous nodules, and the human leukocyte antigen HLA-DR4 [6, 13, 18]. As noted above, there is a growing body of evidence that RA may commence within lung tissue triggered by citrullination of proteins within the lung, a hypothesis supported by the existence of ACPA-positive individuals with pulmonary involvement but no articular disease [29, 30].

RA usually precedes BR by 11–25 years [31, 32]. Markers of RA disease severity [10] and disability do not seem to be associated with RA-BR [31, 32], but evidence is limited because of the absence of well-characterized cohorts and small numbers of patients. No marked differences have been found in immunoglobulin levels, autoantibody status, or complement levels in patients with RA-BR, compared with those with RA or BR alone [33]. Genetic susceptibility studies have again been limited by low numbers. One study found that the frequencies of HLA variants DQB1*0601, DQB1*0301, DQB1*0201, and DQA1*0501 were increased in subjects with BR, with or without RA [34]. Another study showed that DRB1*0401, but not other RA-linked alleles, was significantly associated with RA-BR [35]. These results, however, require replication in larger cohorts.

It is not clear whether there is a direct association between smoking and RA-ILD or RA-BR. Some studies that concluded a link between smoking and RA-ILD actually presented the association between smoking and abnormal pulmonary function tests (PFTs), which can be difficult to interpret in this context [36]. Any association may additionally be mediated by seropositive status associated with ILD. More recent studies have failed to demonstrate a direct association between smoking and ILD [24, 37]. An association between RA-BR and smoking has not been demonstrated, although evidence is limited [38–40]. However, smoking may be an important risk factor for infections and hence poorer outcomes in such patients, which is discussed later in this review.

**Clinical Features Specific to Patients with RA**

Whilst a proportion of RA patients may have subclinical ILD on HRCT and may be asymptomatic, the majority of patients with clinical ILD will present with exertional dyspnea, with or without a dry cough. Examination findings may include bibasal crepitations; however, finger clubbing is relatively unusual [41]. Symptoms of BR include wheeze, productive cough, copious amounts of sputum, hemoptysis, and pleuritic chest pain. There are no clinical features specific to RA-BR [42]. RA, ILD, and BR are all risk factors for RTI [43], suggesting that management of infection risk is particularly important in patients with overlap of these conditions.

**Long-Term Assessment and Management of RA-ILD/RA-BR**

**Assessment**

A thorough baseline assessment of pulmonary disease severity should include clinical features, PFTs, and imaging pattern/extent on HRCT—a high radiological fibrosis score on HRCT being a predictor of poor survival [44–46]. Such objective measures, repeated over time, allow a more accurate representation of disease trajectory and may help inform management decisions. Once
the trajectory is established the frequency of monitoring can be adjusted accordingly [47].

Clinical assessment should include quantification of exercise tolerance using instruments such as the five-point Medical Research Council (MRC) breathlessness scale [48] and the 6-min-walk test [49]. Reduced walk distance and oxygen desaturation below 88% are poor prognostic factors in idiopathic ILD [50, 51]. PFTs should be performed in all patients with respiratory clinical features, confirmed RA-ILD, or prior to decisions about therapy. Low baseline forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) (FVC <60% and DLCO <40% of predicted values) are independent predictors of early death in patients with idiopathic ILD [45, 46]. Importantly, a 6–12 months decline in FVC of at least 10%, or a decline in DLCO of at least 15%, is associated with increased mortality in idiopathic ILD [47, 52] (Box 1, Fig. 1).

**Box 1 Recommendations for clinical assessment**

Quantification of exercise tolerance using instruments such as the five-point Medical Research Council (MRC) breathlessness scale and the 6-min-walk test

- Oxygen saturations of <88% indicate poor prognosis
- Pulmonary function tests at regular intervals: frequency directed by disease trajectory (Fig. 1)
  - Forced vital capacity (FVC) <60% and diffusing capacity of the lungs for carbon monoxide (DLCO) <40% predicted indicate poor prognosis
  - 6–12 months decline in FVC of ≥10%, or a decline in DLCO of ≥15%, is associated with increased mortality

RA-ILD: imaging using HRCT to evaluate extent of fibrosis and subtype

- 20% lung involvement and usual interstitial pneumonia indicate poor prognosis

HRCT imaging is indicated in patients with clinical features of lung disease or in asymptomatic patients with a DLCO of less than 70% of predicted [53]. Individuals with HRCT findings consistent with usual interstitial pneumonia (UIP—basal dominant honeycomb cysts with little or no ground-glass change) have poorer prognosis than those with HRCT-detected features indicative of other types of idiopathic interstitial pneumonia (IIP) [54, 55]. There is no HRCT-based scoring in RA-ILD, although a small study suggested that the degree of interstitial changes detected was predictive of prognosis [56]. On the basis of these factors, a framework for assessment of RA-ILD has been proposed, focusing on risk assessment before initiation of biologic therapy and post-treatment monitoring [47] (Fig. 1). The approach is designed to help predict short-term progression irrespective of therapy. In the absence of clear evidence, such an approach, based on potential risk, may also be useful in RA-BR patients on DMARDs.

The possibility of underlying immune deficiency, particularly antibody deficiency, should be considered in with patients with RA-BR [57].

**Management**

There are no international guidelines on the management of RA-ILD or RA-BR because of limited evidence [58]. In the absence of such consensus, management of moderate to severe lung disease in patients with RA should be in collaboration with a respiratory physician. Given the association with markers of RA disease severity, the management of RA-ILD should include a focus on minimizing RA disease activity. Since the prognosis of RA-ILD is rather poor, a treatment which stabilizes the condition with no further deterioration may be viewed as successful.

Whilst several medications have been used in the management of RA-ILD and RA-BR, there are no randomized controlled trials (RCT) with conclusive evidence of benefit. Glucocorticoids have been used in the context of specific histological subtypes of RA-ILD such as non-specific interstitial pneumonia (NSIP), based on limited evidence from IPF. In steroid-responsive patients, azathioprine was traditionally thought to be of potential benefit [59]. However, the PANTHER trial [60], which evaluated response to the combination of
prednisolone, azathioprine, and N-acetylcysteine in patients with mild to moderate IPF, was prematurely stopped. Compared to placebo, a greater mortality (8 vs. 1 deaths), more hospitalizations (23 vs. 7), and more serious adverse events (24 vs. 8) were observed in the exposed group. Indeed use of glucocorticoids is associated with a significantly increased risk of infection in a dose-dependent fashion [61] (Table 1). Therefore, glucocorticoids should be used sparingly—at the lowest possible dose and the shortest duration—especially in patients with RA-ILD or RA-BR with a higher baseline infection risk.

Rituximab (RTX) appears promising in the treatment of connective tissue disease-related ILD [62–64]. Data on the use of RTX in the treatment of RA lung disease are limited. The evidence, thus far, has not been encouraging in RA-ILD or RA-BR. In an open-label pilot study of ten patients with RA-ILD treated with RTX [65], one patient died of acute respiratory distress syndrome (ARDS)/possible pneumonia, 6 weeks post-treatment (no infective source identified). Of the seven patients who completed the 48-week follow-up, only one showed improvement in respiratory function, five were stable, and one deteriorated. Observational evidence in both RA-ILD and RA-BR has been inconclusive with no clear beneficial effect on disease progression or survival [66–69].
Table 1  Serious respiratory adverse events reported with drugs used in the treatment of rheumatoid arthritis

| Medication | Possible adverse event | Details |
|------------|------------------------|---------|
| Glucocorticoids | Infections [61, 80] | Dose and duration of treatment related to infection risk |
| | | Co-prescription of bDMARDs may further increase risk |
| csDMARDS | Methotrexate | Pneumonitis [81–83] |
| | | Possible increase in infections [84, 85] (poorer response to pneumococcal vaccination) |
| | Pulmonary lymphoproliferative disease [73, 74] | |
| | Leflunomide | Pneumonitis [86, 87] |
| | | Progression of pulmonary nodules [88] with/without pneumothorax [89] |
| | Sulfasalazine | Pneumonitis [90, 91] |
| | | Eosinophilic pneumonias most commonly reported [92, 93] |
| | | Also reported with DRESS [94, 95] |
| | Hydroxychloroquine | Rare cases of pneumonitis and DRESS reported [96–98] |
| bDMARDS | TNFis | Infection such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and opportunistic infections (*Mycobacterium tuberculosis*, non-tuberculous mycobacteria, *Mycoplasma*, *Legionella*, *Pneumocystis jirovecii*) [99] |
| | | Pneumonitis [79] |
| | | Congestive heart failure [100] |
| | | Noninfectious granulomatous disease, e.g., sarcoidosis [101, 102] |
| | | Pulmonary vasculitis [75, 103] |
| | Rituximab | Rapidly progressive pneumonitis [104–106] |
| | | Infection (including opportunistic) [107] |
| | Abatacept | Rare reports of pneumonitis [108] |
| | | Infection (including opportunistic) [107] |
Pirfenidone, an anti-fibrotic treatment, has demonstrated efficacy in IPF [70, 71] and has been approved by the National Institute of Health and Care Excellence in the UK and the FDA in the USA for use in patients with mild or moderate IPF. A phase II study of pirfenidone in RA-ILD is about to start [72].

The emphasis in RA-BR patients should be to minimize risk of infection. RA-BR patients with sputum production may benefit from mucolytics. According to British Thoracic Society guidelines, use of prophylactic antibiotics should be guided by sputum culture and can be considered in BR patients who have frequent exacerbations (≥3 per annum) or serious infections requiring antibiotics or hospitalization [57]. Additionally those with reversible airways disease may benefit from a trial of inhaled corticosteroids [22]. Such decisions should be made under the joint care of a respiratory physician and rheumatologist. In RA-BR patients producing more than 20 ml of purulent sputum over a 24-h period, chest physiotherapy (including self-taught airway clearance techniques) and postural drainage may be considered [57].

It is important that all RA patients with pulmonary disease (and indeed all RA patients) should be regularly immunized against influenza and pneumococcus (see “Respiratory Infection”).

In summary, we suggest that RA-ILD or RA-BR patients who require changes in treatment for their joint disease or ongoing monitoring of their respiratory status should be under the joint care of a respiratory physician and rheumatologist. Treatment decisions should involve a multidisciplinary approach as well as a careful discussion with the patient regarding the benefits and risks of treatment options available.

### Serious Respiratory Adverse Events Following Treatment

The occurrence of serious respiratory adverse events (SRAEs) following commencement of RA treatment may be due to exacerbation of underlying lung disease, drug-induced ILD, or to other pulmonary complications (Table 1). Thorough investigation of the underlying etiology of SRAEs is essential as it can direct further management. A comprehensive evaluation for infection is imperative, especially in patients on high glucocorticoid doses, csDMARDs, bDMARDs, or targeted synthetic DMARDs (covered in the next section). Rare reported associations of therapies are important to consider in patients with atypical presentations (summarized in Table 1). For example lymphoproliferative disease (including non-Hodgkin’s lymphoma) has been described with methotrexate (MTX) treatment and may regress following withdrawal [73, 74]. Paradoxical adverse events such as sarcoidosis and vasculitis have been reported with tumor necrosis factor inhibitors (TNFis) [75, 76].

| Medication | Possible adverse event | Details |
|------------|------------------------|---------|
| Tocilizumab | Pneumonitis [109] | |
| | Infection (including opportunistic) [107] | |
| tsDMARDs | | |
| Tofacitinib | Infection (including opportunistic) [110] | Rare cases of incident ILD and sarcoidosis [111, 112] |

*bDMARDs* biologic disease-modifying antirheumatic drugs, *DRESS* drug reaction with eosinophilia and systemic symptoms, *ILD* interstitial lung disease, *nbDMARDs* non-biologic disease-modifying antirheumatic drugs, *tsDMARDs* targeted synthetic disease-modifying antirheumatic drugs.
“Pneumonitis” has been described with almost every drug used in the treatment of RA, emphasizing the importance of trying to disentangle whether the clinical features are due to infection, an exacerbation, or development of co-existent RA-ILD, or pulmonary disease triggered by the drug. In MTX-treated patients, diagnostic uncertainty and the lack of a gold standard test for MTX-pneumonitis leaves ambiguity about the true pattern of disease. For both MTX and leflunomide (LEF), the risk of incident lung disease in treated RCT patients appears reassuringly low from recent systematic reviews in RA patients [77]. Whilst a full critical review of drug-induced ILD is outside the scope of this paper, we signpost the reader to other reviews on this topic [47, 78, 79].

**RESPIRATORY TRACT INFECTIONS**

**Respiratory Infection**

Respiratory tract infection or community-acquired pneumonia (CAP) is the most common type of infection seen in patients with RA [113], accounting for almost 50% of RA hospital admissions for infection [114, 115].

**Predictors/Risk Factors**

The increased risk of CAP seen in RA is thought to be multifactorial because of patient-related, disease-related, and treatment-related factors (Table 2).

Cigarette smoking may contribute to the excess risk of CAP seen in patients with RA [8] both by increasing the disease severity of RA and by a direct effect on the lungs.

The risk of developing pneumonia in RA rises with increasing disease severity [116]. This may be due in part to physical immobility and in part to immune dysregulation [118, 119]. RA patients demonstrate a reduced response to influenza vaccination compared to healthy controls. This is not affected by the use of prednisolone or DMARDs [120].

**Clinical Features Specific to Patients with RA**

There are no specific clinical features of CAP in patients with RA. However, the mortality rate for CAP is significantly higher compared to patients without RA [115, 121] (22.2% vs. 5.7%).

**Conventional Synthetic Disease-Modifying Antirheumatic Drugs and RTI**

The potential that medication may increase the risk of infection is of great importance to patients. It is known that fear of side effects, such as infection, reduces adherence which is associated with reduced response [122, 123].

The use of csDMARDs may predispose to infection via the adverse event of pancytopenia, particularly in patients with renal impairment [124]. Both LEF and MTX have been shown to impair neutrophil chemotaxis [85] and both are associated with an increased risk of infection. Of all antirheumatic medications, glucocorticoids are associated with the greatest increased risk of infection. There is an established dose-dependent risk of RTI associated with glucocorticoid therapy [80].

The majority of studies investigating the link between csDMARDs and RTI were observational studies and their results must be interpreted with caution. Although observational studies have the advantage of reflecting clinical practice they may also demonstrate channelling bias due to non-random assignment to therapy as a result of physician concerns about infection.

**Biologic Agents and Respiratory Tract Infection**

bDMARD use and the risk of RTI has been the subject of great debate in the literature. A meta-analysis using pooled data from RCTs which investigated the risk of serious infections in patients treated with TNFis [adalimumab (ADA), etanercept (ETN), and infliximab (INF)] found no significant increase in serious infection risk related to TNFi use (OR 1.21, 95% CI 1.09–1.34) [125]. However, the strict inclusion criteria of RCTs...
mean that the patients enrolled in trials are often substantially healthier than those who eventually receive the treatment once licensed. National registries were established to monitor the outcomes of biologic treatment in “real-life” patients. The British Society for Rheumatology Biologics Register (BSRBR-RA) found an increased risk of serious infections in RA patients treated with TNFi (vs. those treated with csDMARDs) (OR 1.2, 95% CI 1.1–1.5) but there was no subgroup analysis for pneumonia [126]. The risk of infection appeared to be highest in the first 6 months of therapy. An increased risk of infection was also demonstrated in the Dutch DREAM registry in which the majority of infections (38.8%) occurred in the respiratory tract [127]. The Italian GISEA registry reported that the risk of infection was higher in patients treated with INF or ADA compared to those treated with ETN (HRadj = 2.24, 95% CI 1.12–4.42 and 4.91, 95% CI 2.71–8.91, respectively) [128].

Some patients prescribed RTX develop hypogammaglobulinemia, which may persist and which is associated with a trend towards higher rates of serious infections [129, 130]. It is recommended that immunoglobulin levels are checked before commencing and 4–6 months after RTX infusions and before any retreatment [131].

### Table 2 Risk factors for respiratory infection in patients with RA

| Risk factor                        | Level of risk                                                                 |
|------------------------------------|-------------------------------------------------------------------------------|
| Male gender                        | 36% RA admitted patients with CAP were male vs. 26% RA non-admitted patients, P = 0.022 [115] |
| Older age                          | Mean age in RA with CAP vs. general population with CAP (years) 71 vs. 61 [115]          |
| Lower education level (per year)   | HR 0.9 (95% CI 0.9–1.0) [116]                                                   |
| Ever smoking (vs. never smoking)   | HR 1.3 (95% CI 1.1–1.5) [116]                                                   |
| Diabetes mellitus                  | HR 2.0 (95% CI 1.6–2.5) [116]                                                   |
| Past medical history of pulmonary disease | HR 3.8 (95% CI 3.2–4.4) [116]                                      |
| Myocardial infarction              | HR 2.1 (95% CI 1.7–2.6) [116]                                                   |
| Comorbidity score                  | HR 1.3 (95% CI 1.2–1.3) [116]                                                   |
| RA duration (per year)             | HR 1.1 (95% CI 1.0–1.2) [116]                                                   |
| Number of previous DMARDs          | HR 1.1 (95% CI 1.1–1.2) [116]                                                   |
| HAQ (per unit increase)            | HR 2.0 (95% CI 1.8–2.2) [116]                                                   |
| MTX                                | No evidence of association [115, 116]                                             |
| LEF                                | RR 1.16 (95% CI 1.02–1.33) [117]                                                  |
| Sulfasalazine                      | No evidence of association [116, 117]                                             |
| Hydroxychloroquine                 | No evidence of association [116, 117]                                             |
| Glucocorticoids                    | HR 1.7 (95% CI 1.5–21) [116]                                                     |
| TNFi                               | HR 2.07 (95% CI 2.37–3.08) [117]                                                  |
|                                    | No evidence of association [116, 117]                                             |

RA rheumatoid arthritis, CAP community-acquired pneumonia, HR hazard ratio, HAQ health assessment questionnaire, MTX methotrexate, LEF leflunomide, TNFi tumor necrosis factor inhibitor
A meta-analysis of trial data and an observational epidemiological study found the incidence rates of hospitalized pneumonia to be similar in RA patients prescribed abatacept and RA patients prescribed csDMARDs [132]. There are limited data on the risk of RTI in RA patients treated with the newer biologics (certolizumab, golimumab, and tocilizumab).

Evidence-Based Management of CAP (Box 2)

Prevention
Consideration of the risk of serious infection, including CAP, should be undertaken prior to the commencement of immunosuppressives. Immunosuppressives should not be prescribed in patients with current serious infections [133]. A previous history of hospitalized infection is associated with an increased risk of bacterial infection requiring hospitalization in patients prescribed DMARDs [134]. The German RABBIT registry used data from 5044 RA patients and a replication cohort of 2990 to develop and evaluate a risk assessment tool which can be used to estimate the probability of a serious infection within 12 months of commencing DMARDs [135]. This tool demonstrates the high risk of infection conferred by the use of high dose glucocorticoids. For those patients with high disease activity but with a high risk of serious infections, clinicians may wish to consider commencing patients on combination csDMARDs rather than TNFi, or consider the use of bDMARDs associated with a lower incidence of infection, such as ETN or abatacept.

Box 2 Prevention and treatment of CAP and its complications in patients with RA

| RA patient at diagnosis |
|------------------------|
| Consider infection risk of immunosuppressives |
| Offer pneumococcal polysaccharide vaccine 23 as a single dose |
| Offer annual influenza vaccination |
| Aim for lowest glucocorticoid dose to achieve disease remission |

| Development of CAP |
|-------------------|
| Treat CAP as per local guidelines |
| Suspend csDMARDs if antibiotics commenced |
| Suspend bDMARDs if an active, severe infection |
| Recommence immunosuppressives once antibiotics completed and clinical symptoms resolved |

| Development of hematological toxicity |
|--------------------------------------|
| Suspend immunosuppressives |
| MTX: give folic acid rescue therapy |
| LEF: initiate washout |

| Development of AKI |
|--------------------|
| Suspend immunosuppressives |
| MTX: give folic acid rescue therapy |

RA: rheumatoid arthritis; CAP: community acquired pneumonia; csDMARD: conventional synthetic disease modifying anti-rheumatic drug; bDMARD: biologic disease modifying anti-rheumatic drug; MTX: methotrexate; LEF: leflunomide.

[128, 136] Current American College of Rheumatology (ACR) guidelines suggest the use of combination csDMARDs rather than TNFi, or abatacept rather than TNFi, but the level of
evidence is very low [58]. The dose of glucocorticoids should be kept as low as possible in all patients. In the general population, immunization against influenza reduces the incidence of hospital admissions and mortality amongst older patients. Immunization against influenza reduces the incidence of hospital admissions and mortality amongst older (>64 years) patients and in younger adults has an overall effectiveness in preventing disease of 59% (95% CI 51–67) [137, 138]. In patients with rheumatological and other “high-risk” comorbidities, influenza vaccination prevented 39 of 1000 healthy persons from being hospitalized for pneumonia/influenza or dying [139]. Pneumococcal vaccination in older adults reduces the incidence of pneumococcal pneumonia by 64% per 1000 person years (pyr) amongst nursing home residents [140]. Current guidelines regarding influenza and pneumococcal vaccination in patients with RA are summarized in Table 3.

There is evidence of a decline in protection against pneumococcal vaccination over time with an associated increased risk of serious pneumococcal infection [144]. MTX, RTX, and abatacept, but not TNFi, reduce antibody response to the pneumococcal vaccination. We therefore recommend that patients should be vaccinated prior to receiving immunosuppressives wherever possible [145–148]. To date, no studies have evaluated whether there is additional benefit from boosting individuals with RA with a revaccination, but there is evidence for doing so in patients with asplenia or chronic renal disease. We recommend that evaluating the clinical benefit of revaccination of patients with RA after 5 years in reducing pneumococcal infection is considered a research priority [149, 150]. Response to influenza immunization appears to be reduced in patients prescribed TNFi therapy but not MTX [151, 152]. The recommendations summarized in Box 3 are based on these guidelines and the current evidence available.

Box 3 Recommendations for pneumococcal and influenza immunization in patients with RA

- Pneumococcal vaccination should be offered to all patients with RA, regardless of treatment
- Pneumococcal vaccination should preferably take place prior to the commencement of DMARDs
- Pneumococcal revaccination after five years should be offered to patients with chronic renal disease
- Annual influenza vaccination should be offered to all patients with RA, regardless of treatment

Treatmen of Infection

Suspension of DMARD therapy during an infection is controversial. One large study investigating csDMARDs has shown that, while there is an increased risk of hospitalization due to pneumonia, there is no evidence to suggest that this translates to an increased risk of mortality [115, 117]. The effects of continuing or withholding MTX and other DMARDs on the outcomes of CAP have not been studied. We recommend that this should therefore be a priority for future research.

Given the results from real-life data, current guidelines, and ex vivo studies, we recommend continuing immunosuppressive csDMARDS (MTX, LEF, and azathioprine) in those with mild infections that do not require antibiotics. However, in serious infections or those that require antibiotic therapy, we recommend withholding csDMARDs until the antibiotic course has been completed and clinical symptoms resolved. As MTX clearance is via the renal tract, impaired renal function can lead to the accumulation of MTX, increasing the risk of pancytopenia [153]. Given the risk of pancytopenia, patients who develop acute kidney injury with pneumonia and sepsis should be offered folinic acid rescue therapy to prevent MTX toxicity [154]. Patients prescribed LEF who...
develop CAP and hematological toxicity such as neutropenia must stop LEF and a washout protocol should be initiated [154].

Neutropenia (<1.5 x 10^9/L) is a recognized side effect of MTX. However, the clinical benefit of granulocyte colony stimulating factor (G-CSF) to RA patients with febrile neutropenia is yet to be fully investigated and evidence is limited to case series [155, 156]. Some authors advocate the use of G-CSF for patients with drug-induced agranulocytosis (neutrophils <0.5 x 10^9/L), particularly in patients with poor prognostic features (neutrophil count <0.1 x 10^9/L, age over 65 years, severe infection, or multiple comorbidities) [155]. European guidelines for patients with chemotherapy-induced febrile neutropenia state that “G-CSF should not be used routinely as adjunct therapy for the treatment of uncomplicated fever and neutropenia, but may be considered in patients who are at a higher risk of infection-related complications and have prognostic factors that are predictive of poor clinical outcome” [157]. We would therefore recommend that G-CSF is not routinely offered to patients with pneumonitis and drug-induced neutropenia. For patients with poor prognostic factors, such as septic shock, an individual case-by-case discussion involving hematology input should take place.

Guidelines recommend that glucocorticoid doses should be kept to a minimum in patients with RA because of the known association between glucocorticoid use and risk of pneumonia [80]. However, patients on glucocorticoids who develop severe infections may require a temporary increase in steroid dosage to avoid adrenal crisis [158].

Current guidance suggests that TNFi treatment should be suspended in patients with a serious infection (those requiring hospitalization) 

| Guideline authors                         | Influenza | Pneumococcal                                      |
|-------------------------------------------|-----------|---------------------------------------------------|
| BSR [141]                                 | No guidance | Immunization against pneumococcal... might be indicated |
| The Joint Committee on Vaccination and Immunisation (JCVI) [142] | Where immunosuppression occurs because of disease or treatment “It is difficult to define at what level of immunosuppression a patient could be considered to be at a greater risk of the serious consequences of influenza and should be offered influenza vaccination. This decision is best made on an individual basis and left to the patient’s clinician” | Patients immunosuppressed because of disease or treatment should receive a single dose of pneumococcal immunization with pneumococcal polysaccharide vaccine (PPV) 23 |
| EULAR [143]a                             | Strongly considered | Strongly considered but it is not known if and when pneumococcal revaccination should take place |
| ACR [58]b                                | Recommended in patients starting/receiving DMARDs or biologic agents | Recommended in patients starting/receiving DMARDs or biologic agents and a one-time pneumococcal revaccination after 5 years |

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a Vaccination can be administered during the use of DMARDs and anti-TNFs but should ideally be administered 4–6 weeks before starting B cell-depleting biological therapy

b Response to vaccination may be reduced following rituximab therapy
admission or intravenous antibiotics) [133]. RTX is contraindicated in RA patients with active severe infection [159] as is tocilizumab [160].

**OPPORTUNISTIC INFECTIONS**

**Epidemiology**

Rates of mycobacterium tuberculosis (TB) in the general population vary widely internationally and are influenced by age and socioeconomic status. In Sweden, RA patients not treated with biologics had a two-fold increased risk of TB (95% CI 1.2–3.4) compared with the general population [161]. It is unclear whether the increased risk in RA patients not treated with biologics is due to the disease or treatment of the disease with csDMARDs or glucocorticoids.

Opportunistic infections including *Pneumocystis jiroveci*, cryptococcal pneumonia, invasive pulmonary aspergillosis, nocardia, and viral pneumonia caused by cytomegalovirus (CMV) have also been described in patients with RA [99]. It is therefore important that clinicians are aware of the possibility of these diseases and their clinical presentations.

**Predictors/Risk Factors**

Treatment with TNFi is associated with an increased risk of developing TB. TNF plays a vital role in the host defense against TB [162]. Active symptomatic TB in RA patients exposed to TNFi is thought to be due predominantly to reactivation of latent TB [163].

A single case of TB was reported in the first TNFi RCT in 1999 [164]. “Real-world” observational studies soon confirmed that treatment with TNFi was associated with an increased risk of TB. In the BSRBR-RA, a multicenter observational cohort study of RA patients starting bDMARDs, the development of TB was greatest in those treated with INF and ADA and lowest with those treated with ETN [165]. It is now well recognized that ETN is associated with a lower risk of TB compared with INF and ADA [165, 166]. In the Swedish registry, the crude incidence of TB was 118/100,000 pyr; the majority of cases (62%) were extrapulmonary and 10 resulted in death. Screening and treatment of prior TB have been found, by the Spanish Biologics Registry, to result in a 78% reduction in the incidence of TB [167].

Information on the risk of reactivation of TB in patients treated with the newer biologics or tsDMARDs (RTX, abatacept, tocilizumab, certolizumab, golimumab, and tofacitinib) is limited to case reports and RCTs [168, 169]. Interestingly, there is no reported increased risk of TB in patients with lymphoma treated with RTX [170].

**Clinical Features of TB Specific to Patients with RA**

TB that occurs in patients prescribed TNFi is more often extrapulmonary and disseminated at presentation compared with other cases of TB [163].

**Evidence-Based Management of latent TB (Box 4)**

On the basis of the evidence presented, we recommend screening and treatment of patients
with latent TB to prevent reactivation in patients starting TNFi. Treatment of latent TB should be in line with national guidelines. Given the ongoing concern of risk of active TB with immunosuppressive biologics, we recommend that these guidelines are followed for all patients starting bDMARDs. EULAR guidelines suggest the use of RTX in patients with latent TB who have contraindications to the use of chemoprophylaxis [171].

**Box 4** Recommendations for screening and treatment of patients with latent TB commencing bDMARDs

- Prior to commencing biologic therapy, all patients should be screened for mycobacterial infection in accordance with the latest national guidelines
- Active mycobacterial infection needs to be adequately treated before biologic therapy can be started
- Prior to commencing biologic therapy, consideration of prophylactic anti-TB therapy (as directed by the latest National guidelines) should be given to patients with evidence of potential latent disease (e.g., positive tuberculin skin test, positive interferon-gamma release assay, past history of TB or abnormal chest X-ray).
- All patients commenced on biologic therapies should be closely monitored for mycobacterial infections. This should continue for at least 6 months after stopping treatment due to the prolonged elimination phase of the drug
- Patients who develop symptoms suggestive of mycobacterial infections should receive full anti-mycobacterial chemotherapy whilst awaiting confirmatory investigations, but may continue with anti-TNF therapy if clinically indicated.

LUNG CANCER AND OTHER SMOKING-RELATED RESPIRATORY DISEASES

**Epidemiology of Lung Cancer in RA**

In a meta-analysis of 12 observational studies, Smitten et al. reported that, compared to the general population, the overall risk of lung cancer was increased in patients with RA: standardized incidence ratio (SIR) 1.63 (95% CI 1.43, 1.87) [172]. This represents a substantial burden given the high background risk of lung cancer in the general population. Smoking is the strongest risk factor for lung cancer in the general population. The meta-analysis by Smitten et al. did not explore the role of smoking in the incidence of lung cancer in patients with RA. Mercer et al. compared the risk of cancer in 3771 biologic-naïve individuals with RA enrolled by the BSRBR-RA from 2002 to 2009 with the risk in the general population for England [173]. During 13,315 pyrs of follow-up, 46 lung cancers were reported to the National Cancer Registry giving a standardized incidence ratio (SIR) of 2.39 (95% CI 1.75, 3.19). Lung cancer was the most common cancer in this cohort. The risk was increased for men (SIR 2.01; 95% CI 1.15, 3.26) and women (SIR 2.66; 95% CI 1.79, 3.80). Smoking was found to be a risk factor for all cancers combined within this cohort (RR for current smokers (vs. never smokers) 2.66; 95% CI 1.71, 4.15; for former smokers 2.14; 1.43, 3.19).

Joseph et al. conducted a study in 5677 patients with incident RA identified from the UK Clinical Practice Research Datalink (CPRD) [8], of whom 60% were ever smokers and 26% current smokers [8]. Current smokers with incident RA were 23 times more likely to die
from lung cancer than RA patients who had never smoked [subdistribution hazard ratio (SHR) 23.2; 95% CI 5.2–105]). This is of similar magnitude to the risk of smoking in the general population in relation to lung cancer in recent times [13]. Former smokers with RA also had an increased risk of death due to lung cancer compared to never smokers (SHR 7.8; 95% CI 1.7, 35.0) [8].

There is no evidence that any DMARD therapies contribute to the high risk of lung cancer in RA.

**Smoking and COPD in RA**

In a study from the Mayo Clinic, the lifetime risk of developing obstructive lung disease (OLD) (which included COPD, asthma, bronchiectasis, obstructive bronchiolar disorders, and ILD-associated airflow obstruction) was significantly higher in individuals with RA compared to the general population (9.6% vs. 6.2%) (adjusted HR 1.54; 95% CI 1.01, 2.34) [174]. Of the 52 patients who developed OLD, 46 (88%) had COPD. Smoking was the strongest risk factor for the development of OLD in this cohort, followed by RF positivity and male gender. The risk of OLD was more than four times higher in ever than in never smokers (HR 4.38; 95% CI 2.14, 8.99) and nearly three times higher in RF-positive RA independent of smoking status [174, 175]. Steroid use (ever) and DMARD use (ever) were associated with an increased risk of OLD, but MTX use was not. The development of OLD was associated with worse survival (adjusted HR 2.09; 95% CI 1.47, 2.97).

In the study by Joseph et al. from the CPRD, the prevalence of COPD was 1% in never smokers, 7% in former smokers, and 6% in current smokers ($\chi^2 (2) = 36, p < 0.001$) during a mean follow-up of 4.5 years from diagnosis [8].

**Benefit of Smoking Cessation in RA**

Current smoking in RA has been independently linked with higher titers of RF, worse disability, and lower response rates to MTX and TNFi [176, 177]. Joseph et al. found that all-cause mortality fell by 15% for each additional year of smoking cessation in heavy smokers and 10% in former light smokers with RA. The risk of death from respiratory causes fell by 21% per year in former heavy smokers. The risk of death due to RTI fell by 30% for each additional year of smoking cessation in former light smokers with RA [8]. However, there was no observable benefit from smoking cessation with respect to death from lung cancer either for former light or for heavy smokers, nor for RTI in former heavy smokers.

Promoting smoking cessation amongst patients with RA could potentially reduce the risk of CAP and lung cancer for these patients. However, in a large multinational study, almost one-third of rheumatologists and two-thirds of rheumatology nurses reported that they did not give smoking cessation advice to most of their patients [178]. Efforts to develop smoking cessation programmes specific for patients with RA have had mixed success. Harris et al. developed visual materials which emphasized the hazards of smoking in RA [179]. Following a media campaign using these materials, they found a 45% increased awareness amongst RA patients that smoking could interfere with the treatment of RA. The materials did not address the link between smoking and respiratory comorbidity in RA. Aimer et al. identified five factors which were barriers to smoking cessation in a New Zealand RA population: lack of support, limited knowledge of the relationship between smoking and RA, uncontrolled pain, inability to exercise, and using smoking as a coping strategy [180]. They then developed an intervention to address these issues but found, in a small pilot study, that the addition of RA-specific support and information was no more effective than the standard intervention of brief advice plus nicotine replacement therapy [181].

We recommend that RA patients should be asked about their smoking status at every consultation and that smoking cessation advice and further support such as nicotine replacement therapy should be made available [182].
CONCLUSIONS

We have reviewed the evidence concerning the burden and evidence-based management of the most common respiratory comorbidities in RA (interstitial lung disease, bronchiectasis, infection, and lung cancer). We have offered recommendations concerning the management of rheumatoid joint disease in the context of pre-existing lung disease or high risk of respiratory infection or reactivation of latent TB. Often good evidence is missing and we have highlighted areas where further research is needed.

ACKNOWLEDGEMENTS

No funding or sponsorship was received for this study or publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. We acknowledge the contribution of Profs. Will Dixon, Eric Matteson, and Dr Nik Hirani in the development of the original management recommendations for RA-ILD.

Disclosures. Meghna Jane and James Bluett are NIHR academic clinical lecturers in rheumatology. Deborah Symmons has nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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