

Non-infectious pulmonary toxicity of rituximab: a systematic review

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Abstract

Objective. Rituximab (RTX), a B-cell depleting mAb, has been reported to cause pulmonary toxicity in many patients. As the use of this biologic is increasing, we have undertaken a systematic review of the literature to gauge the nature and extent of non-infection-related RTX-induced lung disease.

Methods. A systematic literature review was undertaken to document all reported cases of RTX-associated interstitial lung disease (RTX-ILD), evaluating the epidemiological, clinical, radiological, histopathological, laboratory and management data from the available primary sources. The search was conducted using PubMed, the Cochrane Library and EMBASE up to June 2010 using the terms RTX in the advanced search option without limitations and all relevant publications reviewed manually. In addition, unpublished data from the Food and Drug Administration, the European Medicines Agency and the manufacturer (Roche) were evaluated to complement this search. Identified articles were included if they displayed a potential relationship between the administration of RTX and ILD following exclusion of other likely causes.

Results. A total of 121 cases of potential RTX-ILD were identified from 21 clinical studies/trials, 30 case reports and 10 case series. The most common indication for RTX was diffuse large B-cell lymphoma. RTX-ILD occurred more frequently in male patients and was most common during the fifth and sixth decades of life. In most cases, RTX was part of combination chemotherapy, but in 30 (24.7%) cases it was given as monotherapy. The mean and median number of cycles of RTX before disease onset was four, but cases following the first cycle or as late as the 12th cycle were also identified. The mean time of onset, from the last RTX infusion until symptom development or relevant abnormal radiological change was 30 days (range 0–158 days). Abnormal radiological findings were similar in all patients, with diffuse bilateral lung infiltrates apparent on chest radiographs and/or thoracic CT. Hypoxaemia was seen in all cases and pulmonary function tests were uniformly abnormal with a characteristic diffusion capacity deficit and restrictive ventilatory pattern. RTX-ILD was fatal in 18 cases.

Conclusion. ILD is a rare but potentially fatal complication of RTX therapy. This diagnosis should be considered in any patient who develops respiratory symptoms or new radiographic changes while receiving this biologic agent.

Key words: Rheumatoid arthritis, Biologics, Rituximab, Treatment, Lung disease.

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Submitted 20 April 2011; revised version accepted 12 July 2011.

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Introduction

The introduction of biologic agents into our therapeutic armory has led to a sea change in the management of a variety of medical conditions. This is certainly true for rituximab (RTX), a B-cell-depleting antibody, which is now established as beneficial in conditions as diverse as non-Hodgkin's lymphoma (NHL) and RA [1–4]. The safety of a medication, however, trumps all other considerations

when making treatment decisions. This is critical in the case of biological agents where the target of the intervention often lies within complex biological systems responsible for fundamental physiological functions. The safety of biologic agents including RTX has been addressed in several clinical trials, with the general consensus that these agents are well tolerated and have an acceptable toxicity profile. Nevertheless, rare complications may be missed due to the short-term nature of clinical trials and the enrolment of limited numbers of highly selected participants. Furthermore, toxicity may not necessarily be categorized according to the actual underlying pathological mechanism or system they affect.

Respiratory events have been reported in up to 38% of patients receiving RTX and include cough, bronchospasm, dyspnoea, sinusitis and rhinitis. Likewise, respiratory tract infections have been reported in up to 10% of the patients [5]. More recently case reports have described a number of additional and more concerning RTX-related pulmonary toxicities (Table 1). As the use of RTX is increasing (with over a million patients having been treated to date) such reports are anticipated to rise. Given that anti-TNF- α intervention has been associated with the development and progression of ILD, the concern was raised as to whether this may pertain to other biologic agents [4, 6].

The aim of this systematic literature review (SLR) was to document all reported cases of RTX-associated interstitial lung disease (RTX-ILD), evaluating the epidemiological,

clinical, pathological, laboratory and management data from the available primary sources.

Methods

An SLR was conducted in PubMed, the Cochrane Library and EMBASE for reviews, meta-analyses, randomized controlled trials, clinical trials and studies, case studies and series, published up to June 2010 using the terms RTX in the advanced search option without limitation. The search results were assessed by two independent reviewers to include those that discussed safety or adverse effects of RTX on the basis of the title and abstract. Appropriate articles were further screened based on full-text reviews to select only those reporting lung toxicity and/or pulmonary disease. In addition, manual review of references of all the selected publications was undertaken to complement the search together with published data not identified in the initial search, and with unpublished data from the Food and Drug Administration, the European Medicines Agency and the manufacturer of RTX (Roche).

As causality is often difficult to prove, identified articles were only included if they displayed a clear and potential relationship between RTX and interstitial lung toxicity by excluding other potential causes on the basis of temporal relationships, full clinical and biochemical evaluation and histopathological findings, or at least a failure to exclude drug-induced causality. Another determinant for inclusion

TABLE 1. Diagnoses of pulmonary complications associated with RTX

Diagnosis	No. of cases
IP	64
IP with interstitial fibrosis and desquamative alveolitis	1
IP with interstitial fibrosis	1
IP with granulomata and alveolar lymphocytic infiltrates	1
IP with haemorrhagic bronchiolitis	1
IP with lymphocytic diffuse pneumonia	1
Hypersensitivity pneumonitis with granulomata, alveolar haemorrhage and lymphocytosis	1
Same as above plus eosinophilia and fibrosis	1
Pulmonary fibrosis with pulmonary haemorrhage	1
Pulmonary fibrosis with atelectasis, bronchiectasis and organization	1
Pulmonary fibrosis with alveolar haemorrhage and organizing pneumonia	1
Lung injury-induced ARDS	3
Alveolo-interstitial pneumonia with acute respiratory failure	1
Pulmonary haemorrhage	1
Bronchiolitis organizing pneumonia (BOOP)	17
ILD not specified further	15
Acute fibrinous and organizing pneumonia	1
Desquamative alveolitis and sinusoidal histiocytosis	1
Drug-induced diffuse alveolar damage	1
Pneumonia/pneumonitis without identified or recorded infectious agent	4
Organizing pneumonia with organizing fibrosis	1
Cytokine release syndrome causing lung injury	1
Drug-induced pneumonitis causing acute respiratory failure	1

IP: interstitial pneumonitis.

was the quality of the study, which depended on the reliability of the data in concluding a possible causality and the research methodology. This was analysed by three independent reviewers based on the availability and detail of clinical, histological, laboratory and radiological data, the temporal relationship between treatment and the adverse event, re-challenge results and the exclusion of differential diagnoses of lung toxicity. For each case, demographic data were screened to avoid redundancy.

For each case the following information was extracted:

- (i) Year and type of study.
- (ii) Condition requiring RTX therapy.
- (iii) Patient characteristics (age, gender and location).
- (iv) Treatment regimen (duration, dose per infusion, number of cycles and cumulative dose of RTX, monotherapeutic or part of combination treatment).
- (v) Time-to-onset of respiratory complication (time between last RTX cycle and the presentation of respiratory symptoms, or abnormal radiological findings and diagnosis if asymptomatic).
- (vi) Clinical manifestations (main respiratory and systemic symptoms) and their onset.
- (vii) Radiographic findings [chest X-ray (CXR), high-resolution CT (HRCT) and PET].
- (viii) Pathological process based on clinical examination, pulse oximetry, pulmonary function tests, laboratory features [blood and bronchoalveolar lavage (BAL) cultures/screening] and histological features [open lung biopsy (OLB) or transbronchial lung biopsy, BAL cytology].
- (ix) Management (RTX discontinuation, steroid administration, mechanical ventilation and other management).
- (x) Outcome (full recovery/resolution, partial recovery, persistence, deterioration, disease recurrence on re-challenge or death).

Results

Study and patient characteristics

A total of 121 cases of potential RTX-ILD were identified in 21 clinical studies/trials, 30 case reports and 10 case series in our literature search [1, 7–66]. The most frequent indication for RTX was haematological malignancy followed by autoimmune or rheumatic disease. RTX was used in 54 cases of diffuse large B-cell NHL (DLBC-NHL), 31 cases of NHL (testicular; $n = 1$, parotid, $n = 1$, others not categorized further), 6 cases of follicular NHL (1 with concomitant RA), 2 cases of Hodgkin's disease (HD), 1 case of mixed HD and NHL, 3 cases of mantle cell lymphoma (MCL), 1 case of marginal zone (MZ) lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma, 1 case of MZ lymphoma, 1 case of Waldenstrom's macroglobulinaemia, 2 cases of other indolent lymphoma (not further specified), 6 cases of chronic lymphocytic leukaemia (CLL), 3 cases of immune thrombocytopenic purpura (ITP), 1 case of focal-segmental glomerulosclerosis (FSGS), 3 cases of RA (1 with concomitant Castleman's

disease), 3 cases of SLE (1 with LN), 1 case of graft-vs-host disease (GVHD with concomitant DLBC-NHL), 1 case of chronic antibody-mediated kidney allograft rejection and 1 case of idiopathic nephritic syndrome (Fig. 1). Of the cases reported, 46 were from Asia, 34 from North America, 39 from Europe, 1 from Australia and 1 case of undetermined location (Fig. 2).

The mean age of patients (data available in 80/121 cases) was 59.6 years (range 9–88 years) with a median age of 62 years and interquartile range of 52–69 years. Gender was specified in 92 cases, 52 (56.5%) of whom were male (Fig. 3).

Treatment regimen

In most cases, RTX was administered as part of combination chemotherapy with other cytotoxic agents. In 30 cases, RTX was given as monotherapy (Fig. 4). The mean number of RTX cycles given before disease manifestation was 4.1 cycles (range 1–12 cycles) with a median of 4 cycles and interquartile range of 3–5.5 cycles. In most cases a single cycle consisted of an infusion of 375 mg/m², which for haematological malignancies, was repeated every 2, 3 or 4 weeks. In rheumatic conditions, a single cycle consisted of two 500 mg or 1000 mg i.v. infusions given 2 weeks apart. The maximum number of cycles was 12 for haematological and 2 for rheumatological conditions, giving a total cumulative dose of 4500 mg/m² and 2000 mg, respectively. The average cumulative dose before the onset of symptoms was 1500 mg/m².

Onset of disease

The mean time of onset from the last RTX infusion until respiratory symptoms or detection of radiological abnormality was 30 days (range 0–158 days), with a median of 15 days (interquartile range 7–31 days). For those patients where more detailed data were available, 9 experienced pulmonary effects within hours (hyperacute onset), 7 within days (acute onset) and 55 within weeks/months (chronic onset) (Fig. 5).

Clinical presentation

Data were available regarding respiratory symptoms in 92 cases. Common complaints included dyspnoea (65 cases; 70.7%), fever (37 cases; 40.2%) and cough (30 cases; 32.6%), which was almost invariably dry and non-productive. Other symptoms included fatigue, rigours, wheeze, haemoptysis, skin rash and pleuritic chest pain. In 19 (20.7%) cases, the patients were asymptomatic at the time of diagnosis, with the disease being detected radiologically [either by CT or ¹⁸F-fluoro-deoxy glucose (FDG)-PET]. Examination findings reported for 92 cases were unremarkable in the majority of cases (79; 85.9%), with the exception of diffuse fine inspiratory crackles in 12 (13.0%) cases and digital clubbing in 1 (1.1%) case (Fig. 6).

Radiological findings

The radiological findings were similar in all patients, with the chest radiograph revealing diffuse bilateral lung

Fig. 1 Indications for RTX therapy. DLBCL, diffuse large B cell lymphoma.

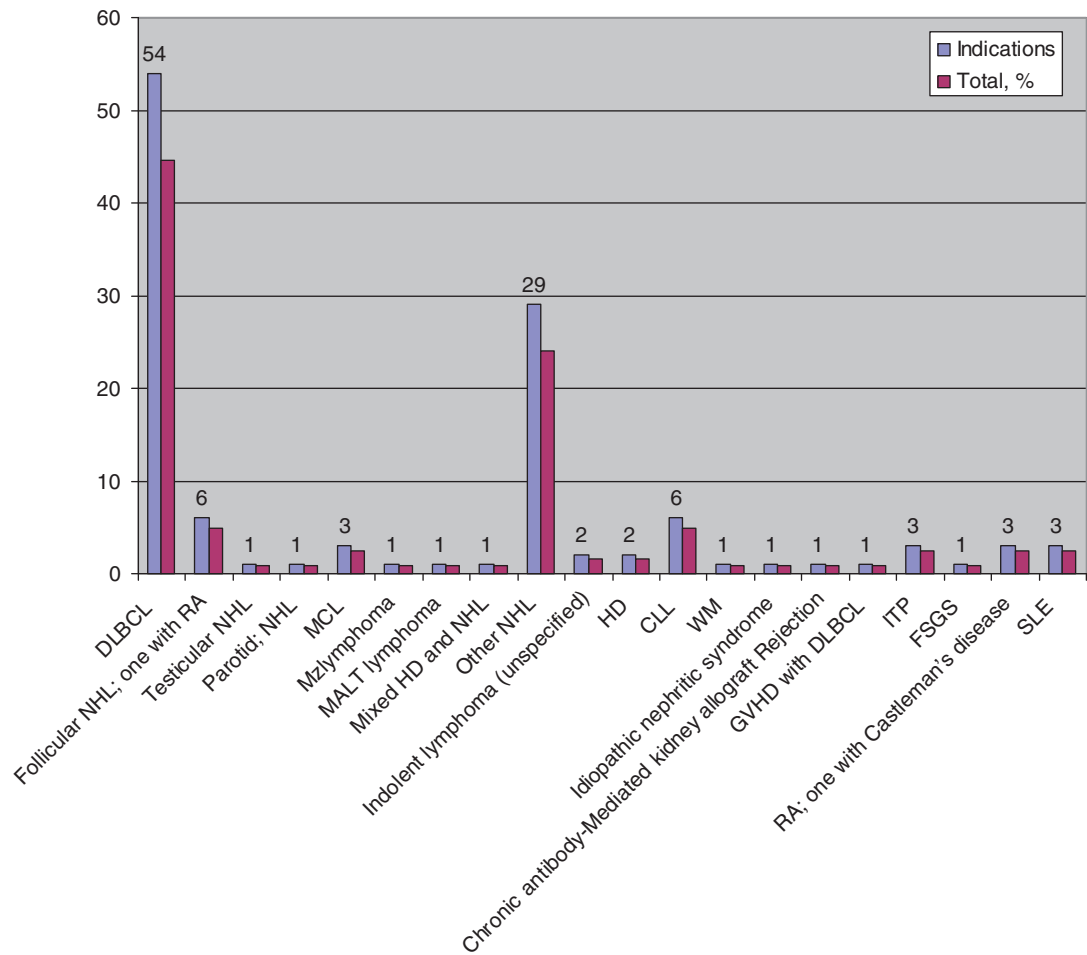
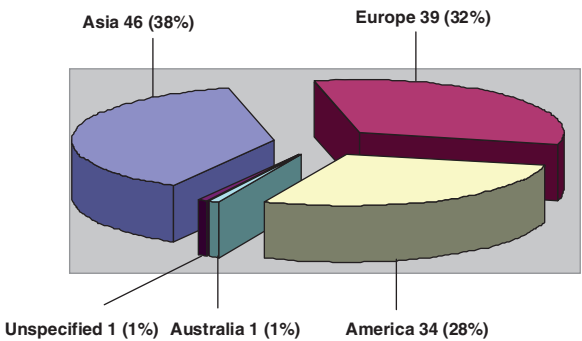
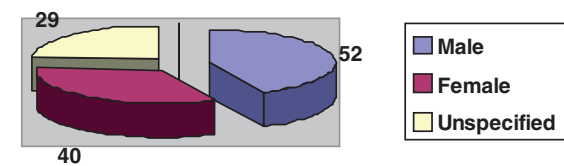


Fig. 2 Case distribution.



infiltrates. These changes were identified in 118 of 121 cases on high-resolution or helical thoracic CT as ground-glass opacification. In some cases, alveolitis, pulmonary fibrosis, alveolar haemorrhage, pleural effusions and consolidation were also described. Where available, PET images (25 cases; 20.7%) were in agreement with the

Fig. 3 Gender distribution.



above, showing the bilateral (rarely unilateral) and diffuse ^{18}F FDG uptake with patchy ^{18}F FDG accumulation in hyper-metabolic lung nodules. Such uptake is indicative of neutrophil activation within the lungs. Interestingly, in 15 cases PET and CT showed radiological abnormalities in asymptomatic individuals, although respiratory symptoms developed typically within days to weeks.

Laboratory and histopathological findings

Hypoxaemia was present in all cases where pulse oximetry or arterial blood gas measurements were performed

(92%). Pulmonary function tests were performed in 29 cases and were uniformly abnormal, displaying a restrictive pattern on spirometry and a significant reduction in carbon monoxide diffusion capacity.

Biopsies were performed in 24 cases, of which 12 were transbronchial biopsy (TBB), 4 were surgical OLB and the remainder were unspecified. Biopsy specimens showed pulmonary inflammation in all cases with additional features of lymphocytic infiltrate ($n=5$), desquamative alveolitis ($n=4$), histiocytosis ($n=2$), interstitial fibrosis ($n=7$), non-necrotic granulomata ($n=3$), organizing pneumonia ($n=7$), atelectasis ($n=1$) and thrombosis ($n=1$). In most cases, extensive bacterial, viral and fungal microbiological investigations were performed, most commonly using BAL, which were uniformly negative. In the few patients studied, there was no evidence of circulating human

anti-chimeric antibodies (HACAs), ICs or other autoantibodies.

Lung pathology

The range of lung pathology reported is given below.

- Bronchiolitis organizing pneumonia/cryptogenic organizing pneumonia.
- Interstitial pneumonitis.
- Hypersensitivity interstitial pneumonitis.
- Idiopathic pulmonary fibrosis.
- Alveolar-interstitial pneumonitis.
- Diffuse alveolar damage.
- Usual interstitial pneumonia.
- Lymphocytic interstitial pneumonitis.
- Desquamative interstitial pneumonia.

Management and outcome

In all cases, RTX was discontinued and CSs were administered immediately. Most patients received concurrent empirical antibiotic and anti-fungal therapy. Outcome data were available in 99 cases, of which 68 patients experienced full recovery, 5 of these recovering spontaneously and without intervention. Nine patients achieved partial recovery with persistent respiratory compromise. RTX-ILD was fatal in 18 cases (Fig. 7).

In patients who improved in association with CS treatment, symptomatic recovery was achieved within days, with radiological resolution lagging behind (weeks to months). Lung infiltrates on CT disappeared within a maximum of 5 months from initial onset. Seventeen patients required mechanical ventilation either immediately or following disease progression, and of these nine died. Two of 10 patients experienced disease recurrence following re-challenge with RTX.

Discussion

The introduction of RTX into clinical practice has altered profoundly the prognosis of patients with a variety of haematological and autoimmune diseases [4, 43, 48, 66–85]. Before this many were destined to receive

Fig. 4 RTX therapy.

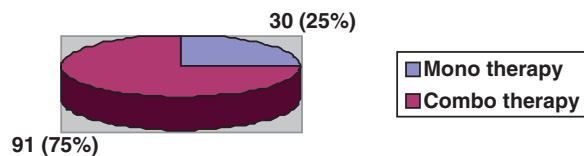


Fig. 5 Disease onset measured from last RTX dose.

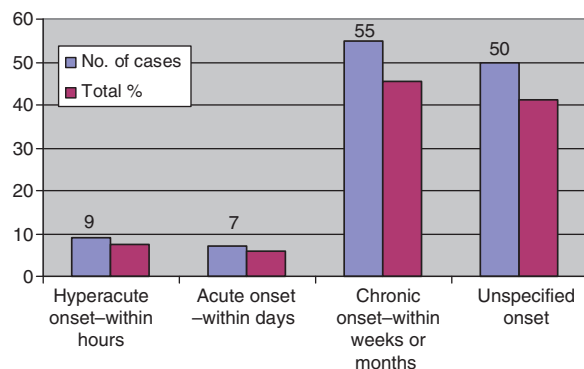


Fig. 6 Clinical presentation ($n=92$).

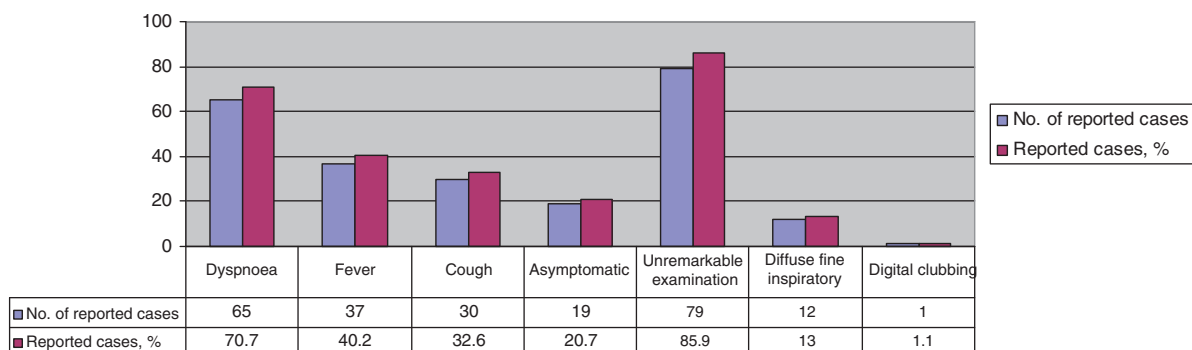
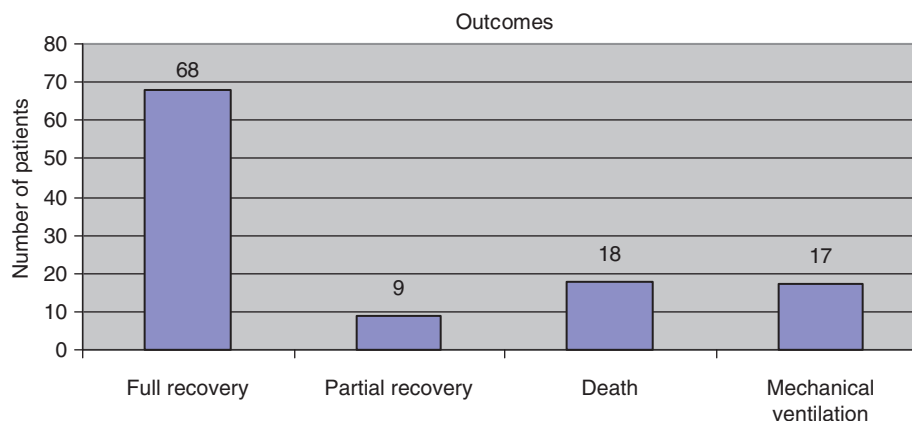


Fig. 7 Outcome data ($n=99$).

medications associated with significant toxicity. Although the overall tolerability and toxicity profile of RTX is good, rare adverse events have been reported, including RTX-ILD. Our SLR was undertaken to identify all cases of drug-induced interstitial lung toxicity after administration of RTX to allow fuller characterization of the potential link between this biological agent and ILD. Our review was extensive and *a priori* in order to limit the potential for selection bias.

Reports of RTX-ILD are rare, with the incidence of this complication being estimated at 0.01–0.03% [11, 25, 86, 87]. Gonzalez *et al.* [87] suggested that lung toxicity could in fact have the highest reporting odds ratio among the adverse effects of this biological agent [relative odds ratio (ROR) 68.1; 95% CI 23.8, 194.9]. Our review has identified a rate of occurrence ranging from 3.7% (1/27 patients) in Kanelli *et al.* [28] to 10.0% (9/90 patients) in Ennishi *et al.* [20], with other reported values in between: 4.0% (8/202 patients) in Coiffier *et al.* [1], 6.2% (8/129 patients vs 1.7%; 1/59 patients in the CHOP only arm) in Katsuya *et al.* [29], 8.0% (4/50 patients) in Brusamolino *et al.* [10] and 8.4% (9/107 patients) in Liu *et al.* [39].

Our review has shown that in clinical studies, especially in the major pre-licensing trials, evaluation of ILD as an adverse effect is often not detailed. This is almost certainly as a consequence of the rarity of the complication and possibly the tighter patient inclusion criteria. Hence, post-marketing reporting provides most of our knowledge regarding RTX-ILD, suggesting that this may be more common and severe than initially reported and associated with a poor prognosis. The true incidence of RTX-ILD may be higher still, as mild disease may be sub-clinical or manifest as bronchitis or pneumonia and hence remain unreported. Failure to diagnose RTX-ILD may lead to symptoms being attributed to infection or progression of the underlying disease. This is especially relevant in diseases such as RA, SLE and primary SS (PSS), where pulmonary complications including ILDs are common [88–91]. Overall, the incidence of ILD is likely to be higher than we have identified and the prognosis worse

due to reporting bias. There is also the possibility of an interaction between pre-existing ILD and RTX treatment in RA; however, our review did not identify this issue mainly due to lack of baseline pulmonary function reporting.

National biologics registers incorporating data from drug regulatory authorities, manufacturers and general post-marketing surveillance will be of great benefit in further documenting this complication. An initial screening history for pulmonary disease, patient education regarding respiratory symptoms as well as an assessment for risk factors of infection would be helpful.

Our study has found that the elderly are at greatest risk of RTX-ILD, with the most common clinical features being dyspnoea, fever and a non-productive cough. Hypoxaemia is invariably present and pulmonary function tests tend to show a restrictive pattern of disease accompanied by a deficit in gas exchange. The rate of onset of disease is usually relatively slow, although there are examples of hyperacute onset manifesting as hypersensitivity pneumonitis or ARDS.

The number of cycles and cumulative dose of RTX do not appear to be related to disease occurrence or outcome. Of note, our review has found that radiological pulmonary changes may be detected while the patient is still asymptomatic. Pulmonary abnormalities on HRCT were bilateral in all and diffuse in the majority of cases. It would appear that ^{18}F FDG-PET is a very sensitive imaging modality to detect this form of ILD and could be used early if this disease is suspected. Interestingly, in a number of cases (16 out of 121; 13.2%), changes on PET were the first indication of RTX-ILD [8, 25, 30, 41, 45, 55, 57, 62]. Patients were asymptomatic for up to 3 months following the detection of PET and CT abnormalities, while others had only mild symptoms at the time of these investigations. Since clinically significant RTX-ILD typically presents as a late complication, appropriate imaging is crucial. With early detection the possibility exists to prevent the development of clinically relevant RTX-ILD with appropriate intervention.

TBB or OLB may be used to confirm the diagnosis and identify the subtype of ILD. Histological features appear very broad and cover an array of pathological categories, but include chronic inflammation and lymphocytic infiltration of the lung parenchyma with cluster of differentiation 4 (CD4) T-cell predominance [52]. As BAL for malignancy or infection was negative in all the cases, this remains useful to narrow the differential diagnoses.

Our review has found a spectrum of RTX-ILD ranging from mild to rapidly fatal disease. Continuation of RTX following the development of symptomatic ILD, as seen in cases where drug-induced lung toxicity was only suspected late, appears to worsen the outcome. High doses of steroids were unable to prevent death in a number of patients. Even among those receiving CSs as part of the RTX regimen, no relationship was found for a more favourable outcome or avoidance of mechanical ventilation or death.

Although a definitive causal relationship between RTX and ILD is difficult to prove, our strict inclusion criteria helped to avoid attributing ILD unjustly to RTX. The main trap in our analysis was the use of concomitant therapies (mostly cytotoxic agents for NHL), which are also known to cause lung toxicity. Our conclusions, however, are reinforced by the fact that there were 30 cases of ILD observed in patients who were treated with RTX monotherapy.

The pathogenic mechanism of RTX-ILD has yet to be elucidated. Owing to the long half life of RTX, prolonged B-cell depletion may interfere with lymphocyte crosstalk, causing cytotoxic T lymphocyte (CTL) dysregulation, thereby promoting lung damage [7, 92]. Leucostasis in the pulmonary circulation [93, 94], release of inflammatory cytokines [11, 95] and cytotoxic substances [96] as well as tumour lysis syndrome [97] are other postulated mechanisms. Obviously, the latter is unlikely in RA patients who do not receive cytotoxic agents.

In any RTX-treated patient who presents with respiratory symptoms, irrespective of the duration of therapy, ILD should be considered and appropriate investigations requested forthwith. These include chest radiograph, arterial blood gas analysis, pulmonary function tests and thoracic HRCT. ¹⁸FDG-PET may be preferable to detect early disease, although access to this imaging modality is limited and costly. Lung biopsy is helpful to confirm the diagnosis and subclassify the parenchymal change. In cases where RTX-ILD is likely (even in early asymptomatic cases), the drug should be stopped and a therapeutic trial of high-dose CSs initiated.

Conclusions

RTX is well established as an effective medication for the treatment of a variety of conditions, including haematological and autoimmune disease. ILD, however, appears to be a rare but potentially fatal complication of RTX therapy. A diagnosis of this should be considered in any patient who develops respiratory symptoms or new radiographic changes while receiving this biologic agent.

Rheumatology key messages

- RTX therapy is associated with rare but potentially life-threatening non-infectious pulmonary complications.
- Clinicians must have a low threshold to investigate new respiratory symptoms or radiological changes.

Acknowledgements

The research in the authors' laboratories is funded by the National Institute for Health Research (NIHR), Cambridge Biomedical Research Centre, Wellcome Trust, Medical Research Council (MRC), Addenbrooke's Charity Trust, Asthma-UK, Biotechnology and Biological Sciences Research Council (BBSRC), Intensive Care Society and Papworth Hospital, National Health Service (NHS) Foundation Trust R&D Department.

Disclosure statement: A.J.K.Ö. has received support from (including attendance at conferences), undertakes clinical trials and acts as a consultant to Roche, Chugai, Schering-Plough/MSD, Abbott, Wyeth, BMS, GSK, MerckSerono and UCB. All other authors have declared no conflicts of interest.

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