

Non-infectious pulmonary complications of newer biological agents for rheumatic diseases—a systematic literature review

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Abstract

Objective. Lung disease is commonly encountered in rheumatological practice either as a manifestation of the underlying condition or as a consequence of using disease-modifying therapies. This has been particularly apparent with the TNF- α antagonists and exacerbations of interstitial lung disease (ILD). In view of this, we undertook a review of the current literature to identify non-infectious pulmonary complications associated with the newer biologic agents used for the treatment of rheumatic conditions.

Methods. A systematic literature review (SLR) was conducted using PubMed, the Cochrane Library and EMBASE for reviews, meta-analyses, clinical studies and randomized controlled trials, case studies and series, published up to June 2010 using the terms rituximab (RTX), certolizumab, golimumab (GOL), tocilizumab (TCZ) and abatacept in the advanced search option without limitations. In addition, abstracts from International Rheumatology conferences and unpublished data from the Food and Drug Administration, the European Medicines Agency and drug manufacturers were used to complement our search. References were reviewed manually and only those articles that suggested a potential relationship between the biological agent and lung toxicity, following exclusion of other causes, were included.

Results. Reported non-infectious pulmonary adverse events with TCZ included a fatal exacerbation of RA-associated ILD, new-onset ILD, idiopathic pulmonary fibrosis and allergic pneumonitis, as well as three cases of microbiological culture-negative pneumonia. Although RTX had a higher incidence of pulmonary toxicity, only 7 of the 121 cases reported involved rheumatological diseases. GOL treatment was associated with four cases of non-infectious pulmonary toxicity and two cases of pneumonia with negative microbiological studies. There were no episodes of pulmonary toxicity identified for either certolizumab or abatacept.

Conclusion. Our results highlight an association between the use of newer biologic agents (TCZ, RTX and GOL) and the development of non-infectious parenchymal lung disease in patients with RA. Post-marketing surveillance and biologic registries will be critical for detecting further cases of ILD and improving our understanding of the pathophysiology of this process. As the use of these drugs increases, clinicians must remain vigilant for potential pulmonary complications and exercise caution in prescribing biologic therapies, particularly to rheumatological patients with pre-existing ILD.

Key words: Rheumatoid arthritis, Biologics, Lung disease, Anti-TNF, Treatment.

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Introduction

Over the past decade, there has been an exponential rise in the use of biologic disease-modifying agents to treat autoimmune diseases. Such therapies have led to an unprecedented improvement in clinical and functional outcomes, particularly in patients with RA. Current biologic agents licensed for the treatment of RA comprise a

diverse group including the TNF- α inhibitors: infliximab [1], etanercept [2, 3], adalimumab [4], certolizumab [5, 6] and golimumab (GOL) [7]; an IL-6 receptor mAb tocilizumab (TCZ) [8, 9] an IL-1 antagonist anakinra [10, 11]; a T-cell co-stimulation molecule blocker abatacept [12, 13] and a B-cell-depleting antibody rituximab (RTX) [14–17].

These agents are effective in ameliorating the signs, symptoms and radiographic damage associated with RA, resulting in improvements in functionality and quality of life [18]. However, their toxicity profile remains to be fully elucidated. As biologic therapies target key signalling molecules and cells of the immune system, adverse events are not unanticipated. Hence, it is encouraging that several large randomized controlled trials have demonstrated that, overall, these biologic agents are well tolerated [19, 20]. Nevertheless, drug-induced toxicities may not be categorized according to the actual pathological mechanism and systems they affect. Furthermore, rare complications, such as interstitial lung disease (ILD), may not be captured in short-term clinical studies with limited numbers of highly selected participants. A prime example of this is the re-activation of latent tuberculosis infection following anti-TNF- α treatment [21–26], which only became apparent as a result of strict post-marketing surveillance [27].

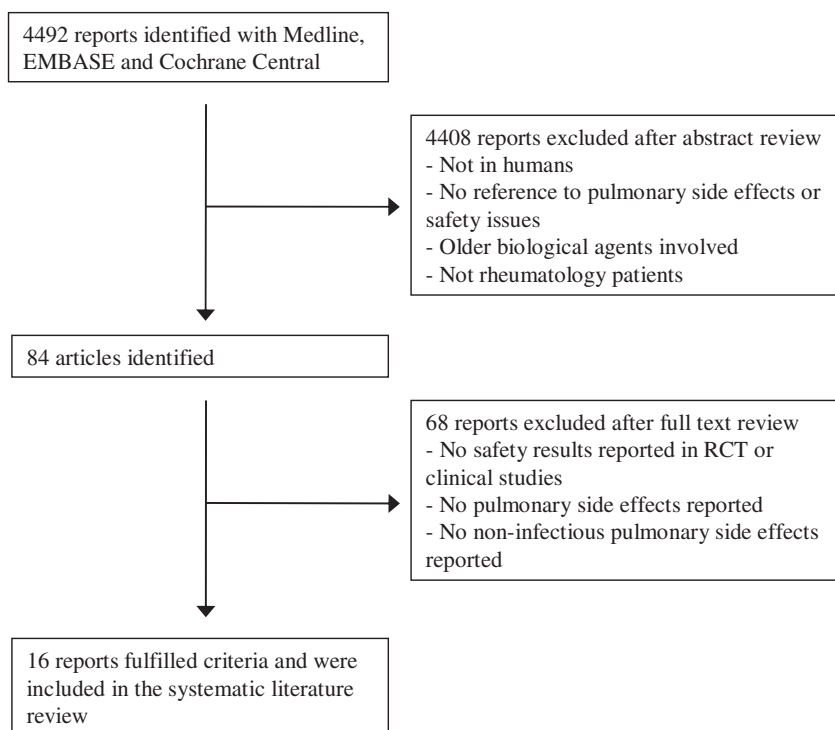
Non-infectious pulmonary complications of the TNF- α inhibitors (infliximab, etanercept and adalimumab) have been well documented and will not be discussed further in this review [28–30]. The aim of this systematic literature review (SLR) was to identify cases of non-infectious lung toxicity, principally ILD, associated with the newer

biologic agents: certolizumab, GOL, TCZ, abatacept and RTX.

Methods

An SLR was conducted using PubMed, the Cochrane Library and EMBASE for reviews, meta-analyses, randomized controlled trials (RCTs), clinical trials, case studies and series, published up to June 2010 using the terms certolizumab, GOL, TCZ, abatacept and RTX in the advanced search option without limitations (Fig. 1). Search results were assessed by two independent reviewers to identify manuscripts that discussed safety with the use of biologic therapies based upon their title and abstract. The selected articles were further screened, based on full-text review, and only those reporting lung toxicity when used for a rheumatic indication were chosen. We also included meeting abstracts from the ACR, European League against Rheumatism web archive and the British Society of Rheumatology Biologics Register newsletter web site. Manual review of these selected publications was undertaken to complement our search as well as unpublished data from the Food and Drug Administration, the European Medicines Agency (EMA) and the drug manufacturers. Identified articles were only included if they reported a possible relationship between the administration of a biologic agent and the development of ILD, having excluded other potential causes, or having failed to exclude drug-induced causality. This analysis was performed by three independent reviewers

Fig. 1 Literature search flow chart.



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 for pulmonary toxicity. In all the RCTs and clinical studies identified, any patient with underlying ILD before the study had been excluded.

For each report, data, if available, were extracted for the following.

- (i) Year and type of study.
- (ii) Condition requiring biologic therapy.
- (iii) Patient demographics (age, gender and locality).
- (iv) Treatment regimen (duration, dose, number of cycles, monotherapy or in combination with other medications).
- (v) Time-to-onset of illness (interval between the last treatment cycle and the development of respiratory symptoms or abnormal radiological findings in asymptomatic individuals).
- (vi) Clinical features (respiratory and systemic symptoms), radiological abnormalities [assessed by chest radiograph (CXR) or high-resolution CT] and investigations [pulse oximetry, pulmonary function tests, blood and sputum cultures, bronchoalveolar lavage (BAL) culture and cytology, and surgical or trans-bronchial lung biopsy].
- (vii) Pathological process/histological diagnosis of pulmonary toxicity.
- (viii) Management (drug discontinuation, mechanical ventilation, CS use and other management).
- (ix) Outcome (full or partial recovery, deterioration, disease recurrence or death).

Results

RTX

Analysis of 65 studies of RTX demonstrated an association with non-infectious pulmonary toxicity in 121 cases; however, only 6 of these cases had an underlying rheumatological condition [3 cases of SLE, 3 cases of RA (1 having concomitant Castleman's disease)]. In one instance, RTX was given for follicular non-Hodgkin lymphoma in a patient with co-existing RA (Table 1). In all other reported incidents, RTX was used for the treatment of haematological malignancy [31–36]. In the Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA trial of 316 patients, only 1 (0.32%) patient developed ILD. All of these were on concomitant MTX treatment; however, none of the 149 controls (on MTX plus RTX placebo) developed any parenchymal lung toxicity.

TCZ

Review of three RCTs of TCZ for the treatment of RA identified non-infectious pulmonary adverse effects in 6 (1.0%) patients out of a total of 589 [37–39] (Table 1). Four out of 419 patients on concomitant MTX therapy developed non-infectious pulmonary adverse effects. Of the remaining two patients, one was receiving SSZ and CSs

and the other was on TCZ monotherapy. However, amongst 323 controls, of which 204 were also on MTX, no parenchymal pulmonary adverse effects were reported. The first case of pneumonia was reported in an RCT performed in 2004. The authors concluded that this represented drug-induced lung toxicity or allergic pneumonitis as no infectious aetiology could be ascertained [38]. Two other episodes of culture-negative pneumonia were reported from the remaining studies, and thus a causal relationship with TCZ could not be excluded. In addition, three cases of parenchymal lung disease, including new-onset ILD, idiopathic pulmonary fibrosis and allergic pneumonitis, were described in these clinical trials. More recently, a fatal exacerbation of RA-associated ILD following TCZ therapy has been documented [40]. This was the only case we identified that was not considered a new-onset ILD.

Storage *et al.* [41] reviewed the safety data from published TCZ clinical trials and found a total of 170 pulmonary adverse effects in the treatment group vs 70 in the placebo group. These included any pulmonary side effects, e.g. cough, wheeze, which were not felt to be infectious in origin. No cases of ILD or parenchymal lung disease were reported in this cohort [41].

GOL

According to the EMA 2009 Assessment Report, serious non-infectious pulmonary adverse events were observed in five Phase 3 trials of GOL for the treatment of RA, AS or PsA, including one case of ILD, two cases of pneumonitis and one case of fibrosing alveolitis [42–46] (Table 1). All of the above occurred in patients receiving GOL and MTX. Furthermore, the Golimumab Before Employing Methotrexate as the First-line Option in the Treatment of Rheumatoid Arthritis of Early Onset study [42] reported two cases of microbiological culture-negative pneumonia in the GOL 100 mg plus MTX group [38]. Six (1.2%) out of 502 patients who developed parenchymal lung toxicity were all receiving MTX. None of the 1129 trial patients on GOL alone developed any parenchymal lung toxicity. None of the 331 on placebo alone developed pulmonary side effects; however, 2/280 (0.71%) patients in the placebo plus MTX control group developed pneumonitis. Therefore, an association with MTX could not be fully excluded for all these episodes. Based upon these data, it is currently unclear if pulmonary complications are associated with GOL monotherapy.

Certolizumab

There have been no reported cases of non-infectious pulmonary adverse events with certolizumab therapy.

Abatacept

Though there is an established association between abatacept and exacerbations of chronic obstructive pulmonary disease [47, 48], our extensive literature search did not identify any other cases of non-infectious pulmonary toxicity, in particular ILD.

TABLE 1 Summary of pulmonary toxicities associated with biologic therapies

Drug	Study	Disease	Treatment protocol and duration	No. of patients on drug	Lung toxicity	Patients on concurrent DMARDs	Radiological or biopsy findings	Management	Outcome
TCZ	RCT [38]	RA	TCZ monotherapy (three cycles); dosage of 8 mg/kg/4 weeks	109	Allergic pneumonitis	None	NA	NA	Hospitalization
TCZ	RCT [39]	RA	TCZ 4 or 8 mg/kg/4 weeks plus MTX	419	One case of IPF, one case of ILD, two cases of pneumonia with no infectious agent identified	All on MTX	NA	Drug discontinued and appropriate treatment	Rapid recovery
TCZ	RCT [37]	RA	TCZ monotherapy; 8 mg/kg/4 weeks	61	Pneumonia with no infectious agent identified	None	NA	NA	NA
TCZ	Case [40]	RA	TCZ 8 mg/kg/4 weeks plus (10 months treatment)	-	Exacerbation of RA-ILD identified	SASP and prednisolone	UIP and emphysema on transbronchial lung biopsy. Exacerbation of existing diffuse, bilateral interstitial lung infiltrates on CXR, ground-glass opacities on CT.	Drug discontinued, steroid pulse therapy and antibiotics	Fatal
RTX	Case [34]	RA and lymphoma	RTX monotherapy (12 cycles); 375 mg/m ² per weekly cycle; total RTX dose of 4500 mg/m ² >12 weeks; adverse effects occurred 3 weeks after last dose of RTX	-	Interstitial fibrosis and organization	None	Diffuse pulmonary infiltrates on CXR. Extensive interstitial fibrosis with focal chronic inflammation on transbronchial and open lung biopsies. Flow cytometry of the lung specimen showed T-cell infiltration (90% of infiltrating cells)	Drug discontinued and high-dose steroids	Fatal
RTX	Case [33]	SLE	RTX monotherapy (one cycle; 1000 mg infusion) with steroid pre-treatment; adverse effects	-	Interstitial pneumonitis	None	Bibasal interstitial opacities on CXR; diffuse, bilateral ground-glass attenuations in on CT.	Drug discontinued and high-dose steroids	Full recovery

(continued)

TABLE 1 Continued

Drug	Study	Disease	Treatment protocol and duration	No. of patients on drug	Lung toxicity	Patients on concurrent DMARDs	Radiological or biopsy findings	Management	Outcome
RTX	Case [35]	RA	4 days after RTX infusion RTX (two cycles; 1000 mg per 2-week cycle; total dose 2000 mg) plus steroids and MTX	-	BOOP	MTX	Bilateral alveolar densities on CXR and CT scan. Videothorascopic lung biopsy showed inflammatory fibrosis	Drug discontinued and high-dose steroids	Full recovery
RTX	Case [35]	RA and Castleman's disease	RTX (four cycles; 500 mg per weekly cycle; total dose 2000 mg)	-	BOOP	HCQ plus steroids	Bilateral perivascular ill-defined alveolar densities and ground-glass opacities on CT scan. Videothorascopic lung biopsy showed inflammatory fibrosis.	Drug discontinued and high-dose steroids	Partial recovery
RTX	RCT [31]	RA	RTX therapy (two cycles; 500 or 1000 mg per cycle) plus MTX	316	ILD	All on MTX	NA	NA	NA
RTX	Clinical study [36]	SLE	RTX monotherapy	15	Pneumonia with no infectious agent identified	None	NA	NA	NA
RTX	Clinical study [32]	SLE nephritis	RTX (two cycles; 1000 mg on Day 1 and on Day 15; total dose 2000 mg) plus prednisone; adverse effect on Day 58 (43 days after last RTX infusion)	72	Interstitial pneumonitis	None	NA	Drug discontinued and high-dose steroids	Fatal
GOL	Five RCTs for RA [42, 44, 45] One RCT for PsA [46] One RCT for AS [43]	Three RCTs for RA [42, 44, 45] One RCT for PsA [46] One RCT for AS [43]	GOL monotherapy 50 or 100 mg $\pm$ MTX depending on trial	1631 (total for all five trials)	One case of ILD, two cases of interstitial pneumonitis, one case of fibrosing alveolitis, two cases of pneumonia with no infectious agent identified	All six patients were also on MTX. In total, 1129 were on GOL alone and 502 were on both GOL and MTX.	NA	NA	NA

SASP: salazosulphapyridine; NA: not applicable; BOOP: bronchiolitis obliterans organizing pneumonia.

Discussion

It is well recognized that patients with rheumatic diseases, such as RA, are at an increased risk of non-infectious pulmonary complications, especially ILD [21, 49]. RA-associated ILD has a diversity of histopathological patterns including usual interstitial pneumonia (UIP) (56%), non-specific interstitial pneumonia (33%) and organizing pneumonia (11%) [50]. The prevalence of ILD in patients with recent-onset RA has been reported to be as high as 8.2% and this feature adversely affects survival accounting for up to 10% of RA-related deaths [51–53]. Several studies have reported smoking, male gender, longstanding RA and high-titre RF as important risk factors for the development of ILD [40, 54, 55]. However, some cases of RA may present *de novo* with isolated pulmonary disease, which suggests that the lung may be involved with the initial immune dysregulation that precedes the systemic inflammatory response [56]. How disease-modifying therapies regulate this inflammatory response and their relationship to the development and exacerbation of ILD is unclear, as is the role of bacterial, viral and fungal infections.

Drug-induced pulmonary toxicity has been described for conventional DMARDs, particularly MTX [57–59], and more recently with the TNF- α antagonists [60]. As these agents may exacerbate RA-associated ILD [27, 61], pre-existing parenchymal lung disease, especially UIP, has been proposed as an additional risk factor [62]. Data from British Society of Rheumatology Biologics Register (BSRBR) suggests that the mortality for RA-associated ILD in patients on anti-TNF agents is 68 deaths/1000 person-years (pyrs) (95% CI 53, 86 pyrs) and 92/1000 pyrs (95% CI 50, 155 pyrs) in the DMARD cohort, generating an age- and sex-adjusted mortality rate ratio (aMRR) of 1.26 (95% CI 0.69, 2.31). After further adjustment for potential confounders, the aMRR fell to 0.81 (95% CI 0.38, 1.73) for the anti-TNF cohort compared with the DMARD cohort [63]. However, there are no data available on the exact incidence of ILD in patients on conventional anti-TNF agents. Our SLR has demonstrated that the newer biologic DMARDs are also associated with non-infectious pulmonary complications, principally ILD, occurring in the context of RA.

The mechanism of lung injury that leads to the development of ILD remains to be determined. While the inflammatory response in RA is Th1 mediated, a Th2 milieu has been implicated in the pathogenesis of several of the ILDs, particularly UIP. This dichotomous response may account in part for the improvement in RA at the expense of worsening ILD [64]. However, it does not explain why only a small number of patients are affected, which suggests that environmental or other immunological factors are involved.

TNF- α has been implicated as a pivotal cytokine in the pathogenesis of pulmonary fibrosis through the modulation of TGF- β , fibroblast proliferation and MMPs to regulate collagen turnover [65–68]. Studies of lung biopsies from patients with idiopathic pulmonary fibrosis have demonstrated TNF- α in macrophages and airway

epithelial cells in areas of fibrosis [69] and blocking TNF- α abrogates bleomycin-induced pulmonary fibrosis in animal models [70]. This would suggest that inhibiting the effects of TNF- α might be beneficial in individuals with RA-associated ILD. However, such global TNF- α blockade may promote cell lysis, leading to the release of macrophage-derived proteolytic enzymes that injure the epithelium and potentiate the fibrotic cascade [64]. Furthermore, perturbing the actions of TNF- α can modulate the pro-inflammatory cytokines IL-1 and IFN- γ to create an environment that favours fibroproliferation and extra-cellular matrix deposition. This is supported by the observation of significantly elevated levels of IL-1 receptor antagonist (IL-1Ra) in the BAL from patients with idiopathic pulmonary fibrosis (IPF) or those who develop bronchiolitis obliterative syndrome following lung transplantation [71]. This prompted us to investigate the association of anakinra, an IL-1 inhibitor, with ILD. Our literature review identified seven reports of ILD, three of which were fatal, associated with this biologic agent [72, 73]. Although this is an interesting observation, it is less relevant to daily practice as anakinra is rarely used for the treatment of RA. At this stage the immunopathogenesis of newer biologic-associated ILD is unknown.

In contrast to the above, we identified several reports of a beneficial effect of newer biologic agents, in particular TCZ and RTX, on connective tissue-associated ILD [74]. This poses an interesting challenge of how to select patients in whom biological therapies will be beneficial rather than detrimental for their co-existing ILD. Careful documentation, radiological characterization and histological classification of the parenchymal lung disease will be essential in helping to unravel this dilemma.

Conclusions

Our review has identified an association between ILD and several of the newer biologic agents (TCZ, RTX and GOL) that are used for the treatment of rheumatological conditions. Determining the immunopathobiology of these non-infectious pulmonary complications will undoubtedly improve our understanding of the disease pathogenesis and may lead to the design of alternative therapies with reduced toxicity. Thus, clinicians should be aware of the ongoing potential risk of ILD in all patients who receive biologic therapies.

Rheumatology key messages

- There is a possible link between newer biologic therapy and the development of non-infectious pulmonary complications.
- Clinicians must exercise caution in prescribing biologics to patients with pre-existing ILD.

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