

# The effect of disease modifying drugs on the lung in patients with rheumatoid arthritis

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## ABSTRACT

*Rheumatoid arthritis (RA) is a systemic inflammatory disease mainly affecting the joints. It has extra-articular manifestations, including lung disease, a major contributor to morbidity and mortality. Careful assessment of systemic signs and symptoms of patients presenting to a pulmonologist with unexplained respiratory symptoms is very important, since RA itself can present with initial pulmonary symptoms without articular manifestations. Several disease modifying agents and biologics have been introduced to treat RA and have been shown to improve the quality of life and slow down the disease progression itself. The possibility of pulmonary toxicity with these drugs has been raised but establishing a causal relationship is difficult. In some case reports stopping the drug in question has reversed radiological changes and decreased inflammatory markers and symptoms, suggesting drug-related toxicity. However, some experts suggest that evolving or increasing pulmonary toxicity usually represents failure of treatment and an indication to switch to a different biologic or disease modifying agent. In this review we evaluate the association between methotrexate, leflunomide, and newer biologic agents and lung disease in patients with rheumatoid arthritis.*

**Key words:** Rheumatoid arthritis, interstitial lung disease, DMARDS, biological drugs

## INTRODUCTION

Rheumatoid arthritis is a multisystem autoimmune disease that can cause several lung diseases; it rarely presents initially in the lungs without obvious joint disease. The medications used to treat RA have adverse effects in the lungs, and it may be difficult to differentiate a progressive rheumatoid lung disease from a new drug-related side effect.<sup>1,2</sup> Treatment decisions critically depend on this distinction. In this review we consider the effects of rheumatoid disease modifying agents on the treatment of rheumatoid-as-

sociated lung disease and their potential to cause adverse drug-related complications in the lung.

## RHEUMATOID ARTHRITIS AND ITS EFFECTS ON LUNGS

One of the most frequent complications of RA involving the lungs is rheumatoid arthritis-related interstitial lung disease (RA-ILD) with an approximate incidence of 10% (Table 1).<sup>3</sup> Lee and colleagues reported that usual interstitial pneumonitis (UIP) is more frequent than nonspecific interstitial pneumonitis (NSIP) in these patients.<sup>4</sup> Pulmonary nodules also develop in RA patients. The exact incidence of nodules is uncertain; they are more common in patients who have long standing RA and who have subcutaneous nod-

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ules. These nodules are usually in subpleural locations and may need to serial follow-up, especially in smokers.<sup>5</sup> Rheumatoid nodules can undergo necrosis causing exudative pleural effusions or pneumothorax. These effusions resemble empyemas on analysis, and infection has to be ruled out.<sup>6</sup> Pleural disease associated with RA can create lung entrapment or a trapped lung. Measurement of pleural pressure can help differentiate these two conditions from each other. Rheumatoid arthritis can also cause cricoarytenoid joint arthritis and affect large airways. These diagnoses require laryngoscopy, flow-volume loops, and computed tomography.<sup>7</sup> Other rare entities seen in the lungs of RA patients are obliterative bronchiolitis (OB) and bronchiectasis.<sup>8,9</sup> Rheumatoid arthritis does not seem to increase the risk of lung infections, but the drugs used to treat RA, which impair the immune system, can increase the risk of infection.<sup>10</sup> Pulmonary hypertension (PH) secondary to rheumatoid vascular disease is rare, but secondary pulmonary hypertension due to underlying heart or lung disease like ILD does occur in RA patients.<sup>11</sup> Dawson and colleagues studied echocardiographic data on 146 patients and found an unusually high incidence of PH (21%).<sup>12</sup>

## **RHEUMATOID ARTHRITIS AND DRUG-RELATED TOXICITY**

It is important to differentiate RA-associated lung disease from drug-induced toxicity since it will change patient management. An excellent source for drug-related lung toxicity is at The Drug-Induced Respiratory Disease Website ([www.pneumotox.com](http://www.pneumotox.com)). Infections are a common complication due to immunosuppressive drug effects, especially corticosteroids.<sup>13</sup> Other disease modifying anti-rheumatic drugs (DMARDs) can suppress immunity, and some of them have direct toxic effects on the lungs (Table 2).<sup>14</sup> These patients usually present with non-specific symptoms, such as dry cough, fever, and progressive shortness of breath. Physical examination varies and may not be helpful. Work-up should include basic laboratory tests, including complete blood counts, brain natriuretic peptide, C-reactive protein, and cultures. Imaging, especially high resolution computed tomography (HRCT), can identify different patterns of parenchymal involve-

ment. Unfortunately, there is no specific radiological pattern associated with any particular drug toxicity. But localization will help plan diagnostic bronchoscopy and broncho-alveolar lavage (BAL). No specific BAL findings confirm drug toxicity. The main purpose of obtaining BAL is to rule out opportunistic infections and alveolar hemorrhage. The treatment of drug-related pulmonary toxicity involves discontinuing the culprit drug and supportive care. If infection is ruled out, a trial of corticosteroids is appropriate.<sup>15</sup> In the following paragraphs we will review literature relevant to drug specific pulmonary toxicity in patients with RA.

## **METHOTREXATE**

Methotrexate (MTX) is probably the most common DMARD used to treat RA. Salliot and colleagues reviewed long term safety of MTX in RA patients. These patients were on MTX monotherapy, and their average dose was 8.8 mg/week with a mean duration of treatment of 36.5 months. Out of 3463 patients, only 15 (0.43%) had pneumonitis directly attributable to MTX.<sup>16</sup> Lung toxicity from MTX may take weeks to months to develop. Alarcon and colleagues analyzed risk factors for MTX-induced toxicity and identified age greater than 60, hypo-albuminemia, diabetes mellitus, prior use of DMARDs, and known lung involvement from RA as significant risk factors.<sup>17,18</sup>

These patients may present acutely, subacutely, or with chronic symptoms.<sup>19</sup> Presenting symptoms include dry cough, shortness of breath, fatigue, and fever. Laboratory work-up is needed to rule out other conditions affecting the lungs, such as congestive heart failure, infections, etc. The most common clinical presentation is subacute and is usually associated with peripheral eosinophilia. The radiological pattern varies, and HRCT is usually required. Radiographic patterns include diffuse ground glass opacities, nodules, and reticular opacities. All these patterns can also be seen with concurrent infection. Bronchiectasis secondary to MTX in RA has been reported. Pulmonary function tests demonstrate a restrictive pattern with volume loss. Bronchoscopy with BAL has non-specific findings but may help exclude or identify infection or malignancy. Transbronchial or open lung biopsy can be considered if the patient has no contra-

indications and does not improve after holding MTX or the diagnosis is uncertain. The histological patterns of MTX-induced toxicity include acute interstitial pneumonia, organizing pneumonia, pulmonary fibrosis, and lymphoproliferative disease.<sup>19,20,21</sup> Infections sec-

ondary to immune suppression with *Pneumocystis jirovecii*, *Nocardia sp*, *Mycobacterium sp*, fungi, and viruses can occur. Treatment requires discontinuing the MTX and supportive care, including systemic corticosteroids, in hypoxic patients.<sup>20,22</sup>

**Table 1 Rheumatoid arthritis related complications in lungs**

RA related complications in lungs	Incidence
<b>Interstitial lung disease</b>	Most common pattern is UIP followed by NSIP, OP, and DAD Overall approximate incidence is 10% (see text)
<b>Airways</b>	Cricoarytenoid arthritis 75% by HRCT but clinically less common. Bronchiectasis 30% by HRCT but clinically less common. Follicular bronchitis and bronchiolitis obliterans (usually with active joint disease or + RF)
<b>Pulmonary hypertension</b>	Clinically rare but systolic PAP > 30 in 26.7% vs. control 4.5% (P=0.03) in one study 21% prevalence by echocardiogram criteria (see text)
<b>Drugs related lung disease</b>	MTX related pneumonitis <1% Leflunomide 0.02-0.48% ( Western vs Japanese cohorts) TNF alpha inhibitors: difficult to predict true incidence but less common (see text) Rituximab related ILD in RA is rare
<b>Pleural disease</b>	5-21% patients have pleuritic symptoms but radiological evidence is less than this. On the other hand autopsy data suggests higher frequency (38-73%)
<b>Lung nodules</b>	0.2-4% depending upon imaging modality (x-ray vs. HRCT) Mostly asymptomatic (see text)

UIP-usual interstitial pneumonitis, NSIP-nonspecific interstitial pneumonitis, DAD- diffuse alveolar damage, OP-organizing Pneumonia, MTX-methotrexate, RF-rheumatoid factor, TNF- tumor necrosis factor, ILD- interstitial lung disease

**Table 2** Pulmonary toxicity associated with disease modifying agents used in rheumatoid arthritis

Non biologic DMARDS	Mechanism of action	Associated pulmonary toxicity	Associated infection	Recommended monitoring
<b>Methotrexate</b>	Folic acid antagonist	Pneumonitis (most common) Fibrosis, nodulosis etc. (Less common)	No reported associated risk; may delay recovery	CBC, LFTs at baseline and then 4-8 weekly initially and less frequently later. CXR at baseline. Dose change may warrant early testing. Pregnancy test at baseline
<b>Leflunomide</b>	Inhibition of lymphocyte pyrimidine synthesis	Interstitial pneumonitis, organizing pneumonia or diffuse alveolar damage (DAD)	Reported associated risk for opportunistic infections	Discontinuation is recommended in severe toxicity or pregnancy
<b>Hydroxychloroquine</b>	Inhibition of antigen processing and costimulatory activity	None reported	N/A	Regular retinal examination recommended due to retinal toxicity at baseline and then 3 monthly
Biologic DMARDS	Mechanism of action	Associated pulmonary toxicity	Associated infection	Recommended monitoring
<b>Infliximab</b>	TNF-alpha inhibitor	Usual interstitial pneumonitis (UIP) (new onset and exacerbations)acute interstitial pneumonitis (AIP) Organizing pneumonia (less common)	Delayed resolution of infections; tuberculosis reactivation, fungal and viral infections	Tuberculosis surveillance (to be done before and periodically during therapy) HBsAg at baseline
<b>Etanercept</b>	TNF-alpha inhibitor	Interstitial lung disease (new onset and exacerbations), common pattern UIP	Delayed resolution of infections; tuberculosis reactivation, fungal and viral infections	Tuberculosis surveillance (to be done before and during therapy) HBsAg at baseline
<b>Adalimumab</b>	TNF-alpha inhibitor	Interstitial lung disease (new onset and exacerbations) UIP	Delayed resolution of infections; tuberculosis reactivation, fungal and viral infections	Tuberculosis surveillance (to be done before and during therapy) HBsAg at baseline
<b>Rituximab</b>	CD20+ B cells	Rare, organizing pneumonia (OP).New onset ILD reported during treatment of lymphomas; possible positive impact on RA-associated ILD	No significant increase in infections; possible JC virus reactivation	IgG levels HBsAg and anti-HBc at baseline CBC q2-4 monthly ECG during and post infusion if h/o arrhythmias

CBC-complete blood counts, LFT- liver function tests, CXR-chest x-ray, N/A- not applicable, HBsAg- hepatitis B surface antigen, IgG- immunoglobulin G, HBc- hepatitis B core antigen, ECG- electrocardiogram, ILD- interstitial lung disease

## LEFLUNOMIDE

Leflunomide is associated with infections, ILD, and less often pulmonary nodulosis.<sup>23</sup> Some of the patients started on leflunomide have had either a pre-existing ILD or MTX-induced lung toxicity.<sup>24</sup> Therefore, it has been thought that the reported increased incidence of leflunomide-related lung toxicity may be a result of a channeling bias. Suissa and colleagues conducted a population based epidemiologic study and found that the risk of ILD is not increased in patients who do not have pre-existing ILD or who have not had MTX-related lung toxicity. They also found that the patients with ILD were twice as likely to be put on leflunomide.<sup>25</sup> The main radiological findings are bilateral ground glass opacities, honeycombing, reticular opacities, and less commonly focal infiltrates. Biopsy can show organizing pneumonia, interstitial pneumonitis, or diffuse alveolar damage.<sup>24,26</sup> Case fatality rates associated with leflunomide-related ILD have been variable. A lower rate in a Korean study was probably related to the accurate diagnosis and prompt treatment using corticosteroids and cholestyramine wash out therapy.<sup>27</sup> Low body weight, tobacco abuse, use of a loading dose, and pre-existing ILD have been linked to increased risk of leflunomide-induced lung toxicity. Pre-existing ILD is the most important factor with odds ratio of 8.<sup>17,28</sup> Leflunomide can cause lung nodules and can stimulate the growth of existing nodules. These nodules can cause pneumothorax, and usually regress with discontinuation of leflunomide.<sup>23,29,30</sup> Based on available literature, leflunomide should be avoided in patients with known ILD or MTX-related pulmonary toxicity.

## BIOLOGICAL AGENTS

Tumor necrosis factor  $\alpha$  blockers like etanercept, anti-TNF $\alpha$  monoclonal antibody like adalimumab, dimeric anti-TNF $\alpha$  antibody like infliximab, IL-1 blockers like anakinra, anti-B cell monoclonal antibody like rituximab, and selective T cell activation modulator like abatacept not only improve joint disease but also lung disease due to RA.<sup>31,32</sup> However, there are also case reports of these drugs causing new onset ILD

or exacerbations of existing ILD in RA patients.<sup>33,34</sup> Since these agents are used in severe RA disease and reported ILD cases are rare, it is difficult to determine the exact incidence of drug-related new onset ILD or worsening of pre-existing ILD due to these agents.<sup>35</sup> The largest database of RA patients on biologics comes from the British Society for Rheumatology Biologics Registry (BSRBR). This registry includes over 8000 patients with RA who are on biologics; the purpose of the registry is to monitor the benefits and side effects related to biological drugs for RA.<sup>36</sup> This group can be compared to a parallel group of active RA patients being treated with conventional disease modifying agents. A prospective study on a small subgroup of these patients suggested that biologics do not increase overall mortality, but ILD seems to be a more common cause of death in patients on biologics than in patients on DMARDs.<sup>35,37</sup>

Granulomatous lung disease in patients on biologics, especially TNF $\alpha$  inhibitors, present with cough, shortness of breath, and chest pain; single, multiple, and cavitary nodules has been described in case reports and case series. Discontinuation of these agents resulted in resolution of disease in most of the cases. Rituximab has also been implicated in several cases.<sup>38-43</sup>

## ILD DUE TO BIOLOGICS

TNF $\alpha$  inhibitors, like etanercept and infliximab, have been reported to cause ILD, notably the UIP pattern in small case series and case reports.<sup>44</sup> In patients who had prior UIP, this complication was almost invariably fatal.<sup>45</sup> Some patients taking MTX developed ILD when put on infliximab but responded well to cessation of both agents and initiation of corticosteroids.<sup>46</sup> A large post marketing surveillance study from Japan of patients on etanercept reported that ILD occurred in only 0.6% of patients.<sup>47</sup> Hagiwara and colleagues reported a case of ILD in an elderly patient eight weeks after initiation of etanercept. This patient was on MTX which was stopped prior to starting of etanercept. This complication resolved after discontinuing etanercept and treatment with pred-

nison.48 Abatacept has not been reported to cause ILD, but it increases the risk of infection if combined with TNF $\alpha$  inhibitors.<sup>31,49</sup> Adalimumab-associated ILD has been reported in cases at a lower rate than other TNF $\alpha$  inhibitors, such as etanercept and infliximab.<sup>50</sup>

The Study Group on Autoimmune Diseases of the Spanish Society of Internal Medicine created the BIOGEAS project. They identified 122 cases of biologics associated ILD. The majority of these patients were on TNF $\alpha$  inhibitors (56 on infliximab and 58 on etanercept). Only 3 were on adalimumab. The most common indication for biologic use was RA (89%). Twenty-six cases had biopsy proven ILD. Based on histopathological details of 20 patients, seven had UIP, five organizing pneumonia, six NSIP, one diffuse alveolar damage, and one lymphocytic interstitial pneumonitis. Complete resolution occurred in 21 (40%) cases, partial resolution in 13 (25%), and no resolution in 18 (35%). The mortality rate was 29% (15 patients) during the follow-up. Seventy percent of deceased patients expired during the first 5 weeks after the initiation of biologic agent. Sixty-seven percent of patients who died were older than 65 ( $P = 0.036$ ), and most of these patients had a prior diagnosis of ILD.<sup>34</sup> Certolizumab is a monoclonal antibody to TNF $\alpha$  and has statistically significant beneficial effects in RAPID and FAST4WARD trials in moderate to severe RA patients either in combination with MTX or as monotherapy.<sup>51,52</sup> Glaspole and colleagues have reported the only case of ILD from certolizumab.<sup>53</sup> Recently, Migita and colleagues reported a case of acute exacerbation of ILD from maintenance therapy with certolizumab.<sup>54</sup>

Rituximab, a CD20 monoclonal antibody, is a well-known cause of ILD when used in hematological malignancies. Contrary to this, rituximab-induced ILD in RA patients is not as common.<sup>55,56</sup> Matteson and colleagues reviewed the effect of rituximab on 10 patients with RA-ILD and reported that the disease was more or less stable.<sup>57</sup> Organizing pneumonia has been very rarely reported in patients on rituximab.<sup>56</sup> At least 2 randomized controlled trials have shown anakinra (an interleukin-1 receptor antagonist) alone or in combination with methotrexate is a safe drug for the treatment of moderate to severe RA.<sup>58,59</sup> The

most important adverse effect is fatal infection; the incidence of this complication is much higher with concomitant use of corticosteroids. Interstitial lung disease due to anakinra is a very rare complication. Tocilizumab, an IL-6 monoclonal antibody, is used to treat moderate to severe RA and has been shown to improve outcomes.<sup>60</sup> Very rarely, lung toxicities, including diseases like ILD, fatality from RA-related ILD, granulomatous disease like sarcoidosis, organizing pneumonia, and exacerbation of combined pulmonary fibrosis and emphysema syndrome, have been reported during tocilizumab therapy for RA.<sup>61-64</sup>

## **TREATMENT OF DRUG-RELATED ILD IN RA PATIENTS**

Establishing a causal relationship between drugs used to treat rheumatoid arthritis and parenchymal lung disease can be very difficult. This is especially true when managing a single patient. These patients may have progressive rheumatoid arthritis with extra-articular manifestations in the lung, subclinical pneumonitis that flares during transitions in therapy regimens, subclinical pneumonitis secondary to prior methotrexate treatment with a predisposition to drug-related lung injury, or definite drug-related injury independent of other disease and treatment factors. However, once ILD due to drug toxicity is suspected, the first step is to withhold the suspected causative agent. Second, it is crucial to exclude other possible complications, such as infection, RA-related ILD, etc. History, pretreatment records, trends in inflammatory biomarkers, and prior radiological studies are helpful in patient evaluation. Supportive care with supplemental oxygen should be provided when needed. Patients should be followed closely with x-ray studies, laboratory tests, and lung function tests until the current problem resolves. Other DMARDs should also be held at this point. Alternate agents to treat underlying RA should be started after the patient starts to improve. Corticosteroids are reserved for very severe ILD and patients who do not improve despite withholding the offending agent or who have a proven diagnosis, such as drug-induced hypersensitivity pneumonitis, organizing pneumonia, or acute

eosinophilic pneumonia. Rechallenge with the same drug is not recommended.

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