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Leflunomide-induced interstitial lung disease (a systematic review)

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Abstract. *Background:* Leflunomide, a disease modifying anti-rheumatic drug in use since 1998, causes interstitial lung disease (ILD) and other pulmonary complications. *Methods:* We undertook a systematic review of literature of PubMed (March 2013) to identify the published literature pertaining to pulmonary toxicity associated with leflunomide. *Results:* We identified 41 relevant articles detailing four population studies and case reports/series on an additional 42 patients. Available data were reviewed and summarized. *Conclusions:* Leflunomide can cause ILD. Most of these patients present within three months of starting leflunomide with acute symptoms for a week or less. Bilateral ground glass opacities and diffuse alveolar damage are the most common radiologic and histopathologic findings, respectively. Patients with pre-existing ILD are particularly at risk for this complication, and leflunomide should be avoided in this population. Activated charcoal and cholestyramine significantly decrease the half-life of the drug because of its enterohepatic circulation and should be considered in cases with acute toxicity. (*Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 167-176*)

Key words: Interstitial lung disease, Leflunomide, Drug toxicity, Drug induced

Main document

Background

Leflunomide is a heterocyclic oral pro-drug of active compound teriflunomide (A77-1726), was licensed as a disease modifying anti-rheumatic drug (Arava, Sanofi US, Bridgewater, NJ) in 1998, and is available in more than 70 countries (1, 2). Leflunomide is cytostatic and exerts its therapeutic effect by reversible inhibition of dihydroorotate dehydrogenase and inhibition of tyrosine kinase (3). Inhibition of dihydroorotate dehydrogenase results in G1 cycle arrest of the lymphocytes (4). Leflunomide also decreases macrophage numbers in tissue, decreases tissue metalloproteinase levels, and decreases neutrophil number and activity (3). Leflunomide increases the production of anti-inflammatory TGF-b, inhibits the production of pro-inflammatory TNF-a and interleukin 1-b , and also inhibits immunoglobulin synthesis, nuclear factor-k-B, cyclooxygenase activity, and growth factor B1 (3, 4).

Leflunomide can be administered at a loading dose of 100 mg/day for three consecutive days, followed by a maintenance dose of 10-20 mg/day (5). It is rapidly converted to teriflunomide during first

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pass metabolism in the gut wall and liver after oral administration (3). Oral bio-availability is 80%, and plasma levels of teriflunomide peak 6-12 hours after oral administration (4). Half (48.2%) of teriflunomide is excreted in the intestine and reabsorbed, entering the enterohepatic circulation, thus prolonging the half-life of teriflunomide to as long as 16.3 ±3.41 days (5). Administration of cholestyramine blocks the enterohepatic circulation and shortens the half-life of teriflunomide to 22.5 hours (5). Forty-eight percent of teriflunomide is excreted in the urine (5). This increases the half-life of the active drug in patients with renal insufficiency.

Three double blind, randomized, controlled trials in adults and one trial in pediatric patients established that leflunomide was effective in the treatment of rheumatoid arthritis (6-9). Since then, leflunomide has also been used for other indications, including sarcoidosis, psoriatic arthritis, SLE, granulomatosis with polyangiitis, Crohn's disease, Takayasu arteritis, ankylosing spondylitis, Felty's syndrome, bullous pemphigoid, polyoma BK virus nephropathy, and as an anti-rejection drug for renal transplants (4, 10-13). Approximately half of patients are withdrawn from leflunomide treatment due to side effects, usually in the first six months of therapy (3). The most common adverse effects associated with leflunomide are gastrointestinal symptoms (diarrhea, dyspepsia, nausea, vomiting, abdominal pain, oral ulcers), abnormal liver function tests, drug eruptions, alopecia, infections, weight loss, and hypertension (3, 14). Myelosuppression with anemia, leukopenia, or thrombocytopenia may occur (4). Serious adverse events associated with leflunomide are comparable to those with methotrexate and sulfasalazine (3).

Sanofi-Aventis Japan issued a safety information notice regarding the relationship between pre-existing interstitial lung disease (ILD) and leflunomide-induced ILD (Lef-ILD) in January 2004 (15). We recently treated two patients who had an exacerbation of their underlying interstitial lung disease after they were switched from methotrexate to leflunomide. A thorough workup excluded other causes for the clinical and radiologic worsening, which was attributed to leflunomide. There are no published data on the current prescription patterns or physician preferences on leflunomide use in patients with ILD, but it is possible that leflunomide is used in these patients because physicians consider it safer than methotrexate. However, this is the patient population in which leflunomide should be avoided because of an increased risk of Lef-ILD and death. We performed a systematic review and analyzed the available literature on the clinical presentation, risk factors, diagnosis, and treatment of Lef-ILD and on the relationship between pre-existing ILD and Lef-ILD.

Methods

A literature search using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) (1966-2013) was finalized on March 10, 2013. The number of articles identified while searching "all fields" and "all dates" using combinations of different search terms including "leflunomide", "lung", "pulmonary", "toxicity", "complications", "pneumonia" and "interstitial lung disease". All articles containing clinical, laboratory, or radiologic details on patients with pulmonary adverse effects associated with leflunomide were reviewed. We also reviewed the reference lists from these articles and used the "related articles" algorithm in PubMed to identify additional articles.

Articles in which the articles' authors believed leflunomide caused pulmonary complications were included. Articles on infectious pulmonary complications associated with leflunomide and with non-specific descriptions of complications such as "ARDS" without specifying etiology (infectious vs. non-infectious) were excluded. Forty-one English language articles were used for this review (Figure 1).

Results

Interstitial lung disease associated with leflunomide

Details on 42 patients from case reports and case series (2-14 patients) from 13 publications (16-28), and two larger population studies (29, 30) are summarized in Tables 1, 2, and 3.

Clinical presentation, incidence, risk factors, mortality, outcome, and prognosis

Most patients received leflunomide for rheumatoid arthritis, were approximately 60 years old, were on leflunomide for two to three months before the onset

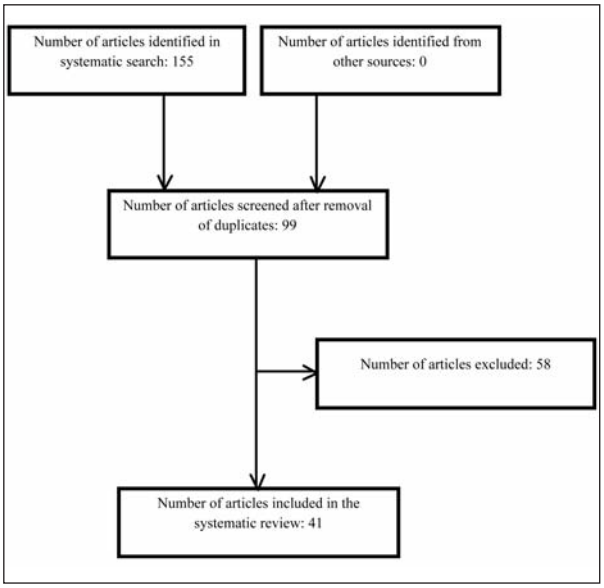

Fig. 1. Literature inclusion flowchart

of symptoms, and presented acutely (within a few days) with dyspnea and cough. Dyspnea (90%), cough (51%), fever (37%), chest pain (5%), and malaise (2%) were the most common presenting symptoms in patients with pulmonary involvement. Thirty-eight percent of these patients developed respiratory failure. Two patients presented two and three weeks after stopping leflunomide, suggesting an occasional time lag between stopping leflunomide and the onset of clinical symptoms.

The prevalence of Lef-ILD appears to be significantly higher in Japan and South Korea than in the Western hemisphere. Low body weight, cigarette smoking, and use of a loading dose increase the risk of Lef-ILD. Overall, 1.2% of the 5054 Japanese patients analyzed by Sawada et al. developed ILD as an adverse reaction to leflunomide (15). Sato et al. analyzed the clinical data on approximately the same patient group more rigorously and found that the incidence of Lef-ILD was somewhere between 0.4%

Table 1. Characteristics of the 42 patients reported in case series/reports

Parameter		Value
Age	Years	62 (9-83)*
Sex	Female	49.5%
	Male	40.5%
Region	East (Japan, Korea, China)	57%
	West (Australia, NZ, UK, USA, Germany)	43%
Indication for leflunomide	Rheumatoid arthritis	81%
	Psoriatic arthritis	2.4%
	Autoimmune nephropathy	16.6%
Duration of underlying condition	Years	7.5 (0.5-25)*
Loading dose of leflunomide used (**18)	Yes	44.4%
	No	55.6%
Maintenance dose of leflunomide (**29)	10 mg po qd	20.7%
	20 mg po qd	75.9%
	Other regimens	3.4%
Duration of leflunomide use (**41)	Weeks	13 (2-133)*
Previous methotrexate use (**41)	Yes	75.6%
	No	24.4%
Concomitant methotrexate use (**42)	Yes	33.3%
	No	66.7%
Pre-existing lung disease (**24)	None	45.8%
	Interstitial lung disease	37.5%
	Other pulmonary diseases	16.7%

** Median (Minimum-Maximum); ** Represents the number of patients out of 42 on which information regarding this particular parameter was provided*

Table 2. Clinical information on the 42 patients reported in case series/reports

Parameter		Value
Duration of symptoms before presentation (**17)	Days	3 (1-30)*
Presenting symptoms (**41)	Dyspnea	90.2%
	Cough	51.2%
	Fever	36.6%
	Chest pain	4.9%
	Malaise	2.4%
Radiographic presentation	Bilateral opacities (**40)	100%
	Ground glass opacities (CT) (**21)	91%
	Interstitial infiltrates (CXR) (**15)	21.4%
	Honeycombing (**42)	14%
	Other findings (CXR) (**23)	35.7%
Respiratory failure (**34)	Yes	38.2%
	No	61.8%
Biopsy done (**8)	Autopsy	37.5%
	Transbronchial	25%
	Surgical	12.5%
	Unknown	12.5%
Histopathology (**8)	Diffuse Alveolar Damage (DAD)	50%
	Other findings	75%
Therapy (**41)	Leflunomide stopped (**40)	97.5%
	Corticosteroids (pulse)	48.8%
	Corticosteroids (any)	70.7%
	Other cytotoxic therapy	7.1%
	Leflunomide removal therapy	34.1%
Outcome (**42)	Died	23.8%
	Recovered/resolved	38.1%
Improved	7.1%	
	No improvement	2.4%
	Survived (details unavailable)	28.6%

** Median (Minimum-Maximum); ** Represents the number of patients out of 42 on which information regarding this particular parameter was provided*

Table 3. Clinical features of patients presenting with leflunomide induced interstitial lung disease

Author	Number	Female (%) of pts.	Age	RA duration (Mean, Yrs)	Leflunomide duration	Symptom duration (Mean, yrs)	Respiratory failure (Mean)	Mortality
Sato et al.(29)	22	63%	67	10	10 weeks	NA	32%	41%
Suissa et al.(30)	74	70%	62	NA	NA	NA	NA	NA
Case reports(16-28)	42	50%	62	7.5	13 weeks	3 days	38%	24%

(22/5780) and 1.1% (61/5780)(29). Ju et al. analyzed data from 1,010 Korean patients diagnosed with rheumatoid arthritis who had been treated with leflunomide for more than a month and identified 10 patients with probable Lef-ILD (17). Savage et al. estimated the reporting rate for Lef-ILD was 0.02% worldwide, between 0.03% and 0.05% in Australia, and between 0.2% and 0.63% in New Zealand (24). These numbers represent reporting rates only without any mention of inclusion and exclusion criteria.

Suissa et al. calculated that 8.1 patients per 10,000 (0.08%) developed Lef-ILD and required hospitalization (30). Possible causes for the differences in incidence of Lef-ILD among different populations include genetic polymorphism common to rheumatoid arthritis associated ILD and Lef-ILD in the Asian population (15) and differences in average body weight between Asian and Caucasian patients (5).

Pre-existing interstitial lung disease was the biggest risk factor for development of leflunomide induced interstitial lung disease, and is discussed separately below. Sawada et al. found that cigarette smoking (OR 3.1, 95%CI 1.7-6.0), low body weight (< 40 kg) (OR 2.9, 95% CI 1.1-7.3), and use of a loading dose for leflunomide (OR 4.0, 95% CI 1.2-12.9) increased the risk of developing Lef-ILD on multivariate analysis (15). Sato et al. found that significant hyoxemia and need for mechanical ventilation predicted mortality (29). Eighty-nine percent of patients who died were hypoxemic (PaO2 < 60 torr or SaO2 of < 90%), compared to 31% of those who survived (p=0.01). Seventy-nine percent of the patients who died required mechanical ventilation, but none of the survivors required mechanical ventilation (p<0.01) (29). Analysis of the 42 patients in case reports/series we collected showed that 46% (6/13) of patients who developed respiratory failure died; none of the patients without respiratory failure died (p=0.01, Chi square test). Forty-seven percent (7/15) of patients presenting with fever died, compared to 12% (3/23) of those presenting without fever (p=0.017, Chi square test). No other factors predicted mortality in these 42 patients.

Radiologic appearance

Diffuse or patchy ground glass opacities or consolidation occur frequently in patients with confirmed or probable Lef-ILD(31). Sakai et al. defined the diffuse alveolar damage (DAD) radiologic pattern as diffuse or patchy foci of consolidation or ground glass opacities with structural distortion, such as traction bronchiectasis, and noted that it was present in eight of seventeen patients with definite or probable Lef-ILD. Seventy five percent of patients with the DAD radiologic pattern died compared to only 11% of those without the DAD radiologic pattern (p=0.056)(31). The presence of structural distortion, such as traction bronchiectasis in the patients with the DAD radiologic pattern, suggests a pre-existing and chronic interstitial process rather than an acute drug-induced process, and these patients with pre-existing ILD likely have a worse prognosis. New infiltrates usually appeared in the upper, anterior, and central lung fields, not in the lower, posterior, and peripheral lung fields, which are usually involved in pre-existing IP associated with underlying RA, and, after recovery, no residual structural derangement was observed in the areas with new infiltrates (1). Analysis of the 42 patients in case reports and case series shows that abnormal radiographic findings were bilateral in all patients and that bilateral ground glass opacities on CT was the most common radiologic finding (Table 2). Interstitial infiltrates on chest radiographs were noted in 21% of patients. Honeycombing was described in six (14%) patients (pre-existing in one patient). Authors for these case reports/series often used nonspecific descriptors such as "reticular pattern", "pneumonitis", and "reticulonodular infiltrates" in the remaining cases.

Histopathology and cytopathology

Diffuse alveolar damage (DAD) was the most common histopathologic finding noted in patients with Lef-ILD, and the histopathological findings in patients, when available, are summarized in Table 4. Cytology profile on the bronchoalveolar lavage was available on only one patient, and the differential showed a lymphocyte predominance (71%) with eosinophils (11%).

Pre-existing interstitial lung disease and leflunomide pulmonary toxicity

Clinical aspects

Sawada et al. reported that pre-existing ILD was the most important risk factor for development of Lef-ILD (OR 8.2, 95% CI for OR 4.6-14.4, p<0.0001)(15). Sato et al. found a trend towards high mortality in patients with pre-existing ILD when these patients developed Lef-ILD (89% mortality for those with pre-existing ILD vs. 46% for those without, p=0.07)(29). Details regarding pre-existing ILD were available on 24 of the 42 patients

Table 4. Histopathologic findings in patients with Leflunomide induced interstitial lung disease

Author	Number	Mode	Outcome	DAD*	Histopathology.
Sato et al.(29)	2	Autopsy	Death	Yes	DAD with organization and exudation. UIP pattern in periphery.
Sato et al.(29)	1	Transbronchial	Survived	No	Alveolitis with lymphocyte infiltration, Masson bodies.
Vallbracht et al.(26)	1	Autopsy	Death	Yes	Chronic interstitial pneumonia and and organization of DAD
Martin et al.(20)	1	Surgical	Survived	No	Hypersensitivity pneumonitis, with granulomas
Wong et al.(27)	1	Transbronchial	Survived	Yes	Thickened alveolar septae by lymphohistiocytic cells
Nesheiwat et al.(21)	1	Transbronchial	Survived	Yes	DAD with organizing pneumonia
Hirabayashi et al.(16)	1	Autopsy	Death	Yes	DAD in organizing phase
Ochi et al.(22)	1	Autopsy	Death	Yes	DAD with organizing pneumonia
Savage et al.(24)	1	Unknown	Survived	No	Acute interstitial pneumonitis

** Diffuse Alveolar Damage*

in our review. Of these 24 patients, nine patients (38%) had pre-existing ILD, and 15 (62%) did not. Fewer patients without previous ILD died (7%) when compared to patients with previous ILD (44%) (p=0.047, Chi square test). Suissa et al. found that leflunomide was associated with an adjusted rate ratio of ILD of 1.9 (95%CI 1.1-3.6), compared to adjusted rate ratios of 1.1, 0.7, and 1.4 for methotrexate, biologic DMARDs, and traditional DMARDs, respectively (30). These authors suggested that the association of ILD with leflunomide was likely from prescription of leflunomide to patients with a history of methotrexate use or pre-existing ILD (30). Ju et al. noted that the public insurance guidelines for leflunomide use in Korea required that this drug be prescribed only after the failure of a first-line DMARD, including methotrexate (17). The Korean patients described by these authors still had a high incidence of Lef-ILD despite the fact that preexisting ILD and a history of methotrexate exposure had not been regarded as indications for the administration of leflunomide (17).

Inokuma et al. noted that the distribution pattern of new radiologic findings and lack of residual structural distortion in these areas of new radiologic findings after resolution suggested that the ILD that developed after starting leflunomide was distinct from the pre-existing ILD in these patients (1). Many patients on leflunomide were on methotrexate prior to leflunomide, and this might implicate methotrexate as the cause of ILD. However, the patients on methotrexate previously developed ILD relatively soon after starting leflunomide regardless of the time on methotrexate, and this suggests that leflunomide rather than methotrexate caused the ILD in these patients (24). Leflunomide is not the only drug that has been reported to cause a worsening of underlying fibrosis in patients with pre-existing ILD. Methotrexate, infliximab, and gefitinib have been implicated in accelerated ILD in patients with pre-existing fibrosis. Infliximab infusions have caused acceleration of underlying rheumatoid ILD and death of some patients (32). These patients were on azathioprine prior to commencement of TNF therapy and had stable lung disease. Pre-existing pulmonary fibrosis significantly increases the risk of worsening of ILD in patients receiving gefitinib (33, 34). Acute methotrexate lung is a well described entity that presents acutely and shares many clinical, radiologic, and histopathologic characteristics with Lef-ILD, including previous ILD as a risk factor for its development (35). These case reports support the conclusion that some drugs can trigger progression of ILD.

Acute exacerbations of rheumatoid induced ILD are quite rare, despite a relatively high prevalence of asymptomatic ILD in patients with rheumatoid arthritis (15). Sawada et al. felt that patients with pre-existing ILD may have been more likely to receive leflunomide, hence the association of ILD with leflunomide (15). However, they noted that the usual time course with acute worsening within six months of starting leflunomide suggests that the drug is the cause for this acute deterioration rather than a flare of the underlying ILD associated with rheumatoid arthritis (15). In addition, rheumatoid arthritis seldom deteriorates into a hyper-acute presentation and DAD (1). Therefore, it seems likely that leflunomide caused ac-

celerated fibrosis in these patients rather than a flare in any underlying ILD associated with rheumatoid arthritis.

Lef-ILD did not occur in a case series of 70 patients with sarcoidosis treated for 16±13 months with leflunomide (13). This study included 70 patients with thoracic sarcoidosis. Eight patients developed complications consistent with pulmonary infection, and leflunomide was continued in six of these patients after treatment(13). Consequently drug-induced pneumonitis seems unlikely. The information in this small study suggests that the pathogenesis of the underlying disease influences the development of Lef-ILD, and the presence of pulmonary infiltrates alone is not necessarily a risk factor for Lef-ILD.

Pathophysiology

The accelerated ILD noted in patients with preexisting pulmonary fibrosis after administering leflunomide has a possible biological explanation. Repeated epithelial cell damage and abnormal wound repair and remodeling resulting in abnormal deposition of extracellular matrix proteins such as collagen are important in the pathogenesis of pulmonary fibrosis (36). Myofibroblasts have an important role in abnormal wound repair and remodeling through various mechanisms, including deregulation of the balance between matrix metallopeptidases (MMPs) and tissue inhibitors of metallopeptidases (TIMPs) (36). Lung epithelial cells undergo epithelial-mesenchymal transition (EMT) to become myofibroblasts after treatment with TGF-b_1 in vitro, in patients with pulmonary fibrosis, and in the lungs of bleomycin treated animals (36). In vitro studies implicate leflunomide in the pathogenesis of pulmonary fibrosis by the induction of EMT of lung epithelial cells (36). Leflunomide stimulates an EMT-like phenomenon in mouse lung in the presence of other fibrosis-inducing stimuli such as bleomycin but does not do this in the absence of these stimuli (36). Mice treated with bleomycin and leflunomide had severe interstitial pulmonary damage, whereas mice treated with leflunomide or bleomycin alone at the same concentrations did not have significant damage at those concentrations (36). Bleomycin induced collagen deposition in lungs, and pulmonary hydroxyproline level are greatly increased in the presence of leflunomide (36). The mortality in these animals treated with bleomycin and leflunomide is significantly higher than animals treated with bleomycin alone (36). Co-administration of uridine suppresses pulmonary tissue damage, collagen deposition, and the increase in pulmonary hydroxyproline levels observed in mice treated with both bleomycin and leflunomide, suggesting that leflunomide exacerbates bleomycin-induced pulmonary fibrosis by inhibiting dihydroorotate dehydrogenase (36).

Treatment

Enterohepatic circulation prolongs the half-life of teriflunomide to one to four weeks (27). Charcoal or cholestyramine can shorten the half-life to approximately one day (27). Cholestyramine given orally at eight grams thrice daily reduces plasma levels by approximately 40% in 24 hours, by 49% - 65% in 48 hours, and to undetectable plasma levels in 11 days (27). Cholestyramine eight grams tid for 11 days should therefore be considered in critically ill patients presenting acutely with leflunomide toxicity. Activated charcoal orally 50 grams every six hours for 24 hours can be given in addition to cholestyramine (4). Plasma exchange has been described as an alternative method to clear the active metabolite (5).

In the Japanese cohort reported by Sato et al., leflunomide was discontinued in all patients (29). An unspecified number of patients received corticosteroids and cholestyramine, and two patients underwent plasmapheresis. No difference in survival or outcomes was noted in patients receiving teriflunomide removal therapy or corticosteroids compared to those who did not (29). The following treatments were used in the 42 patients in the case reports/series. Leflunomide was stopped in 98% of patients. Thirty-four percent of patients underwent leflunomide removal therapy; all these patients received cholestyramine, and one patient received plasma exchange. Seventy-one percent of these patients received corticosteroids, 49% received high doses of corticosteroids (details not provided by the authors), and seven percent of these patients were treated with other cytotoxic therapy (cyclophosphamide). We recommend that leflunomide should be stopped immediately in all patients suspected to have significant toxicity. Cholestyramine should be considered in all patients with acute and/or severe leflunomide toxicity. Activated charcoal is an alter-

native to cholestyramine. Plasmapheresis can be considered in patients with acute and severe toxicity in whom the other removal therapies cannot be administered, but probably cannot be recommended as the first line therapy. Corticosteroids should probably be considered in patients presenting with acute severe toxicity.

Sources and quality of data

Sources, quality of data, and criteria used to diagnose Lef- ILD from four studies (15, 29-31) and the larger case series (17, 24, 28) are summarized in Appendix 1. While the aggregated information from all the published data on Lef-ILD provides a reasonably good picture of Lef-ILD and the risk factors, the retrospective nature of the studies, the reporting bias associated with the case reports and case series, and the varying definitions of Lef-ILD are obvious shortcomings which will remain until data from larger multicenter randomized studies become available.

Conclusions

Leflunomide can cause ILD. Most of these patients present within three months of starting leflunomide with acute symptoms for a week or less. Bilateral ground glass opacities and diffuse alveolar damage are the most common radiologic and histopathologic findings, respectively. Patients with pre-existing ILD are particularly at risk for this complication and leflunomide should be avoided in this population. Activated charcoal and cholestyramine significantly decrease the half-life of the drug because of its enterohepatic circulation and should be considered in cases with acute toxicity.

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Appendix 1. Sources, quality of data and criteria used to diagnose leflunomide induced ILD

Author	No. of cases	Study type and region	Data sources	Case definition/criteria used to select patients
Sawada et al.(15)*	61	Retrospective (Japan)	Analysis of case report forms filled by physicians as part of post-market surveillance. Reported as is, no further analysis/selection.	No case definition used by authors. No description of how other disorders were excluded.
Sato et al.(29)*	22	Retrospective (Japan)	Study committee reviewed surveillance sheets, clinical data and radiographic findings of patients thought by treating physician to have Lef-ILD.	Inclusion criteria: presence of newly developed lung disease after leflunomide use, diffuse bilateral distribution and exclusion of other causes including infection. Exclusion criteria: Treating physician opinion that lung injury was unrelated to leflunomide
Sakai et al.(31)*	17	Retrospective (Japan)	Clinical presentation, laboratory tests and radiographs of patients thought by treating physician to have Lef-ILD were examined by pulmonologists, rheumatologist and radiologists	Exact inclusion and exclusion criteria not specified by authors. (Of the 17 cases, 8 classified as definite and remaining 9 probable)
Suissa et al.(30)	74	Retrospective (USA)	Analysis of PharMetrics, a computerized database containing hospitalization and prescription data. 1:100 nested case control study.	Patients who were previously prescribed leflunomide and were hospitalized with diagnoses of postinflammatory fibrosis (code 515), idiopathic fibrosing alveolitis (code 516.3), or other/unspecified alveolar pneumopathies (codes 516.8 and 516.9)
Savage et al.(24)	14	Retrospective (Australia and New Zealand)	Analysis of reports of respiratory disorders occurring in association with leflunomide use, initially reported as part of post-market surveillance.	Searles and McKendry's criteria (Appendix 2) (Information incomplete on many patients)
Zhang et al.(28)	7	Retrospective (China)	Review of Chinese literature for cases with interstitial lung disease after leflunomide use for renal indications, and summary of cases thus identified.	Modified Searles and McKendry's criteria (Appendix 2)
Ju et al.(17)	10	Retrospective (Korea)	Analysis of data on 1010 patients with 7 university hospitals.	Modified Searles and McKendry's criteria (Appendix 2)
Others (16,18-23, 25-27)	11	Case reports	Case reports by treating physicians	Varying definitions and details

** (These three studies describe different aspects of Lef-ILD in the same cohort of approximately 5000 Japanese patients.)*

Appendix 2. Searles and McKendry's diagnostic criteria for methotrexate (hypersensitivity) pneumonitis

Major criteria:

1. Hypersensitivity pneumonitis by histopathology without evidence of pathogenic organisms.
2. Radiologic evidence of pulmonary interstitial or alveolar infiltrates.
3. Blood cultures (if febrile) and initial sputum cultures (if sputum is produced) that are negative for pathogenic organisms.

Minor criteria

1. Shortness of breath for less than 8 weeks.
2. Nonproductive cough.
3. Oxygen saturation 90% on room air at time of initial evaluation.
4. DLCO 70% of predicted for age.
5. Leucocyte count 15 109/L.

Definite pneumonitis – 2 major and 5 minor criteria

Probable pneumonitis – 2 major and 3 minor criteria.