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REVIEW ARTICLE

Proposals for leflunomide use to avoid lung injury in patients with rheumatoid arthritis

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Abstract Among the 5,043 consecutive patients registered in the postmarketing surveillance for leflunomide, 61 were reported to have lung injury and 24 died from it. The adjusted multivariate logistic regression analysis of the risk factors showed that preexisting interstitial lung disease posed the greatest risk, as well as loading dose, smoking history, and low body weight of 40 kg or less with odds ratios of 8.17, 3.97, 3.12, and 2.91, respectively. In 12 patients, lung injury developed even 2 months after leflunomide withdrawal. When patients with ($n = 9$) and without ($n = 13$) fatal outcome were compared, eight out of the former, and six out of the latter had preexisting interstitial lung disease; the former showed severe hypoxemia, high serum C-reactive protein level, hypoalbuminemia, and continuous lymphocytopenia, and required mechanical ventilation. On the basis of these results and literature review, the committee proposes that leflunomide should only be recommended as a second-line drug, should not be administered to patients with preexisting interstitial lung disease, should also not be administered to patients with smoking history or those with low body weight, and should be administered without loading dose. Careful monitoring is necessary, and when lung injury develops, leflunomide elimination using colestyramine is mandatory.

Keywords Leflunomide · Lung injury · Proposals for leflunomide use · Rheumatoid arthritis

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Introduction

Leflunomide was introduced as a disease-modifying antirheumatic drug (DMARD) in September 2003 in Japan, after applying the data of clinical trials obtained in Western countries. The official recommendation was that postmarketing surveillance (PMS) of 2,400 consecutive patients with rheumatoid arthritis (RA) should be reported to the government. At the launch, leflunomide was expected to be safely administered to patients with rheumatoid lung diseases because adverse respiratory reactions had rarely been reported in Western countries and in clinical trials in Japan. However, soon after the launch, pulmonary adverse reactions with a high mortality rate were reported, [1] leading to an emergent safety announcement for leflunomide from the maker, Sanofi-Aventis Japan (formerly Aventis Pharma Japan). After this, the Study Committee for Leflunomide-Induced Lung Injury was organized in the Japan College of Rheumatology, the mission of which is to elucidate the risk factors, clinical characteristics, and factors affecting prognosis, and to recommend proposals for the effective use of leflunomide to avoid leflunomide-induced lung injury. The committee analyzed the data of surveillance obtained from Sanofi-Aventis Japan, in addition, the inquiries send from the committee and answered by the attending physicians and plain chest X-ray or computed tomography (CT) films received from them.

Review of literature on pharmacodynamics, clinical efficacy on arthritis, and adverse reactions of leflunomide, before the launch in Japan

Leflunomide is one of the isoxazole compounds developed by Hoechst AG in the 1970s. Orally administered leflunomide is nonenzymatically converted to the active metabolite A771726 in the blood or liver. A771726 exerts immunosuppressive or antirheumatic effects by inhibiting dihydroorotate dehydrogenase, which is essential for de novo pyrimidine synthesis in activated lymphocytes, and nuclear factor κB.

Leflunomide is designed to be administered at a loading dose of 100 mg/day for three consecutive days, followed by a maintenance dose in the range from 10 to 20 mg/day. The loading increases plasma A771726 concentration more rapidly. When administered at 10 or 20 mg/day after the loading, the mean plasma plateau concentration of A771726 becomes 23.9 or 43.0 μg/mL, respectively [2]. Because half of A771726 (48.2%) is excreted into the intestine [3] and reabsorbed forming enterohepatic circulation, its half-life ranges from 14.9 ± 5.7 to 16.3 ± 3.41 days [4]. Administration of colestyramine blocks the enterohepatic circulation and shortens the half-life of A771726 to 22.5 h [5]. In one healthy volunteer, active charcoal was found to shorten the half-life. A771726 at 42.8% is also recovered from urine [3].

The clinical efficacy of leflunomide is comparable to those of methotrexate and sulphasalazine [6, 7]. When the plasma A771726 concentration exceeds 13 μg/mL, 60% of patients responded well, indicating that the concentration correlates with the efficacy [8]. Phase II dose ranging study conducted in Japan on 256 patients showed that the ACR20 responder rates at week 28 were 27.2%, 47.4%, and 52.6% for patients receiving maintenance daily doses of 5, 10, and 20 mg, respectively [2]. In addition, the inhibitory effect on radiological progression of joint erosion was reported in Western countries [6, 7].

The adverse reactions associated with leflunomide as reported in Western countries included diarrhea (27%), respiratory infection (21%), nausea (13%), headache (13%), rash (12%), liver damage (10%), dyspepsia (10%), and alopecia (9%) [9]. In clinical trials for safety evaluation in Japan, adverse reactions were observed in 248 out of 365 patients (68%), including liver dysfunction (18.6%), diarrhea (10.7%), alopecia (10.7%), urinary sedimentation abnormality (9.6%), rash (9.0%), hypertension (8.2%), and upper respiratory tract infection (8.0%); no induced or deteriorated interstitial pneumonia was observed.

Pulmonary adverse events observed during PMS

Among the 3,625 consecutive patients registered in PMS from the launch to the emergent announcement of leflunomide-induced lung injury (termed Cohort A: from September 2003 to 27 January 2004), 50 patients were reported as possibly having leflunomide-induced lung injury by the attending physicians, and among these, 21 patients died from it (Table 1). The incidence and mortality rate of leflunomide-induced lung injury at that time were

Table 1 Pulmonary adverse events observed during postmarketing surveillance (PMS) of leflunomide for rheumatoid arthritis in Japan

	Cohort A	Cohort B′	Cohort B
Patients registered (with surveillance sheets)	3,625 (3,414)	988 (848)	1,392 (792)
Patients with preexisting lung injury	362 (10.6%)	10 (1.18%)	3 (0.38%)
Patients with newly developed lung injury	50 (1.4%)	7 (0.93%)	4 (0.88%)
Patients who died from lung injury	21	3	0

1.4 and 42%, respectively. After the emergent announcement, a new surveillance sheet with an inquiry concerning preexisting interstitial lung disease was adopted on 23 July 2004 (Cohort B, ongoing). The period between Cohort A and Cohort B was termed Cohort B′. In Cohorts A, B′ and B, 3,625, 988, and 1,392 patients were registered until 9 June 2006, and the surveillance sheets were obtained from 3,414 (94.2%), 848 (85.9%), and 792 (56.9%) patients, respectively. The incidences of preexisting interstitial lung disease in Cohorts A, B′, and B were 10.6, 1.18, and 0.38%, respectively. In Cohorts B′ and B, the numbers of patients with interstitial pneumonia reported as an adverse reaction to leflunomide decreased to seven of 753 (0.93%) and four of 454 (0.88%) patients with available data.

Analysis of pulmonary adverse events

The background features of all patients in Cohorts A, B′ and B whose surveillance sheets were available were analyzed in relation to the development of interstitial pneumonitis, in terms of sex, age, body weight, stage and class of RA, disease duration of arthritis, history and past complications including preexisting interstitial pneumonitis, allergy, smoking, adverse drug reactions, coadministration of other drugs, and loading and maintenance doses of leflunomide [10]. Plasma A771726 concentration was not included in the analysis, because the data were scant, and serum albumin level was not as well because the measurement was biased. In 12 patients, lung injury developed even 2 months after leflunomide withdrawal.

According to the results of univariate analysis, male gender, age older than 60 years, body weight lower than 40 kg, preexisting interstitial lung disease, smoking, and loading dose were found to be risk factors for leflunomide-induced lung disease. When adjusted multivariate logistic regression analysis was adopted, preexisting interstitial lung disease, loading dose, smoking history, and low body weight were confirmed as risk factors, with odds ratios of 8.17, 3.97, 3.12, and 2.91, respectively (Table 2). Among them, preexisting interstitial lung disease was found to be the most clearly significant ($P < 0.0001$) risk factor for the injury.

Table 2 Odds ratio of risk factors of leflunomide-induced lung injury found by multivariate logistic regression analysis

	Preexisting interstitial lung disease	Loading dose	Smoking history	Low body weight
Odds ratio	8.17	3.97	3.12	2.91

Laboratory data obtained at the lung injury onset showed increased levels of serum C-reactive protein (CRP) (11.6 ± 8.1 mg/dL: mean ± standard deviation) and lactate dehydrogenase (LDH) (482.2 ± 347.0 IU/L) and decreased peripheral blood lymphocyte count (760 ± 437/μL). The CRP level decreased once after leflunomide administration (from 3.6 ± 3.0 to 1.0 ± 0.9 mg/dL, $P < 0.01$) and then reincreased at the lung injury onset (from 1.0 ± 0.9 to 11.6 ± 8.1 mg/dL, $P < 0.01$). Lung injury developed 138.1 ± 174.7 (6–1,204) days after the start of leflunomide administration. In 12 patients, it developed 2–110 (22.8 ± 30.2) days after stopping leflunomide administration. In a patient who was administered colestyramine immediately after leflunomide withdrawal, the plasma A771726 concentration decreased to half after about 1.5 days. A771726 levels of the three patients who received plasma exchange were measured, but were already low after the use of cholestylamine.

Among the 5,054 patients of all the cohorts, 67 were reported to have pulmonary infections. Eight patients had bacterial infection, seven *Pneumocystis* pneumonia, four mycobacterial infection, one cytomegaloviral infection, and one fungal pneumonia, and 46 had pneumonia of unknown origin.

Comparison between patients with and without fatal outcome

To elucidate the factors for the poor prognosis of patients with leflunomide-induced lung injury, the characteristic of the patients who died of and those of patients who recovered from the injury were compared [11].

The chest X-ray or CT films and surveillance sheets of the 47 patients, out of the 61, were submitted to the committee. Among these 47, 31 were presumed to have leflunomide-induced lung injury after the committee examined their precisely described charts and available images. Among these 31 patients, 13 recovered (Group R), nine died of the injury (Group D), and nine died of other causes including pneumothorax ($n = 3$), abscess ($n = 2$), *Pneumocystis* pneumonia ($n = 1$), hemophagocytic syndrome ($n = 1$), tracheal injury ($n = 1$), or an unknown cause other than leflunomide-induced injury from which the patients were recovering ($n = 1$).

The patients with fatal outcome were older and predominantly male, and mostly had preexisting interstitial pneumonia (88.9 vs. 46.2%, $P = 0.07$), although none of these factors showed any statistically significant difference. The number of patients who received a loading dose, the mean maintenance dose, and the mean plasma A771726 concentration at the lung injury onset did not differ between the groups. However, patients with fatal outcome

significantly more frequently showed hypoxemia of less than 60 Torr of arterial blood oxygen pressure or less than 90% of oxygen saturation level (88.9 vs. 30.8%, $P = 0.01$), a lower serum albumin level (2.7 ± 0.6 vs. 3.3 ± 0.5 g/dL, $P = 0.03$), and a higher serum CRP level (19.3 ± 9.4 vs. 10.1 ± 8.1 mg/dL, $P = 0.03$), and required mechanical ventilation (77.8 vs. 0%, $P<0.01$). Both groups had elevated LDH and KL-6 levels and lymphocytopenia (711 ± 566 vs. 894 ± 455/μL, $P = 0.42$) at the lung injury onset. In Group D, the lymphocyte count remained low; in contrast, it recovered after the improvement of lung injury in Group R (406 ± 396 vs. 1,203 ± 399/μL, $P<0.01$). Diffuse bilateral ground glass opacities (GGOs) on chest X-ray or CT films appeared to overwhelm the lung fields, including the anterior and upper lung fields, which sometimes contained airbronchogram and sometimes showed lobular mosaic or geographical pattern in both groups. Steroid therapy and drug removal therapy were similar for both groups, but only Group R patients responded well.

The main histopathological finding in two autopsied patients was diffuse alveolar damage with hyalin membrane formation and its organization, and preexisting fibrosis, [12] in contrast to lymphocytic alveolitis and intraalveolar fibrosis, without preexisting fibrosis in the biopsied lung of a patient who recovered.

Table 3 Cautions for leflunomide use to avoid lung injury

1. Leflunomide is recommended for active rheumatoid arthritis when the-first line DMARDs are ineffective.
2. Leflunomide should not be administered to patients having preexisting interstitial lung diseases. It should also not be administered to patients with smoking history, and low body weight. Leflunomide prescription should be restrained for patients with male gender, age older than 60 years, impaired lung function, or renal dysfunction.
3. A loading dose is not recommended. Instead, gradually increasing the dose is recommended.
4. Careful monitoring for respiratory signs and symptoms is mandatory, including examination of chest X-ray images prior to the start of leflunomide treatment, and regular monitoring of arterial blood oxygen saturation. Laboratory tests include those for levels of serum CRP and LDH, and peripheral blood lymphocyte count. Observation is necessary at least until 2 months after the withdrawal of leflunomide.
5. If lung injury develops, differential diagnoses include pulmonary infections, rheumatoid lung disease, and other drug-induced lung injuries. Opportunistic infections, particularly *Pneumocystis* pneumonia, should be carefully differentiated.
6. If leflunomide-induced lung injury is likely, leflunomide withdrawal and colestyramine administration should be immediate; active charcoal or plasma exchange might be good alternatives. Steroid administration is recommended for moderate to severe cases. Empiric therapy for *Pneumocystis* should also be considered. In patients with respiratory failure or with markedly increased CRP level or decreased albumin level, intensive supportive treatments for the respiratory system are indispensable.

Proposals for leflunomide use to avoid lung injury

Mainly on the basis of these analyses and literature review, the committee formulated proposals for the proper use of leflunomide for RA to avoid leflunomide-induced lung injury (Table 3). The proposals provide information on indication and contraindication, physical and laboratory examinations that should be conducted during the therapy, differential diagnoses to be considered, and treatment for leflunomide-induced lung injury.

Leflunomide should be considered in active RA patients resistant to level-A DMARDs recommended by the study group of the Japanese Ministry of Health, Labor, and Welfare, which include methotrexate, sulphasalazine, or bucillamine [13]. Leflunomide should not be administered to patients with preexisting interstitial lung disease. Attending physicians should examine it by auscultation and plain chest X-ray and, when interstitial lung disease is suspected, chest CT images should be examined before the start of leflunomide treatment. Leflunomide should also not be administered to patients with smoking history, those with a substantially low body weight, such as less than 40 kg. Leflunomide prescription should be restrained for male patients older than 60 years. Administration of loading dose is instructed in the appended document of leflunomide, [3] but the committee does not recommend loading because loading dose was one of the significant risk factors of leflunomide-induced lung injury; instead, increasing the dose to a necessary but smaller maintenance dose is recommended. We also suggest that leflunomide should not be administered to patients with impaired lung function even if the impairment is not caused by interstitial lung diseases, because such patients hardly survive from leflunomide-induced lung injury. Leflunomide should not be administered to patients with renal dysfunction as well, because over 40% of A771726 is excreted in urine.

After leflunomide treatment is started, careful monitoring of the patient is required. Monitoring includes interview concerning respiratory symptoms, physical examination including auscultation, measurement of body temperature and arterial blood oxygen saturation, laboratory examination of serum CRP and LDH levels, peripheral blood lymphocyte count, and examination of chest X-ray or CT images if necessary. It should be noted that leflunomide-induced lung injury can develop even 2 months after stopping leflunomide administration. Careful observation of clinical courses would be helpful. The typical clinical course is as follows: the patient initially responds well to leflunomide, with arthritis improving with a decrease in

CRP level; thereafter, the CRP level reincreases with the appearance of respiratory signs or symptoms sometimes with or without fever, and without the arthritis worsening, with a decrease in lymphocyte count. It is noteworthy that lymphocytopenia, which lasted in the case without recovery, is a common finding to leflunomide- and methotrexate-induced lung injury [14].

Differential diagnoses include pulmonary infection, rheumatoid lung disease, and other drug-induced lung injuries. Among these, a diffuse pulmonary infection particularly *Pneumocystis* pneumonia is important, because it and leflunomide-induced lung injury have common radiological features such as GGOs with a mosaic or geographic pattern. Measurement of serum β-D-glucan level is necessary, and sputum cytology and polymerase chain reaction analysis of sputum for *Pneumocystis* would be helpful. If the diagnosis of *Pneumocystis* pneumonia is difficult to confirm, empiric anti-*Pneumocystis* pneumonia therapy should be considered in patients with severe respiratory failure. Measurement of cytomegalovirus antigenemia is also necessary for differentiation. Only with images it is difficult to differentiate leflunomide-induced lung from other drug-induced one, because no GGO pattern specific to leflunomide was observed.

Once lung injury is highly suspected during or even after stopping leflunomide therapy, the removal of A771727 from the plasma is the first line of treatment that should be immediately performed. Its withdrawal should be started by administering 8 g of colestyramine three times a day as a standard treatment. When colestyramine is not immediately available, active charcoal administration or plasma exchange may be good alternatives. The efficacy of steroid therapy for leflunomide-induced lung injury is uncertain, but steroid therapy including pulsed infusion is strongly recommended for moderate to severe cases as a supportive therapy for respiratory distress. Empiric antimicrobial therapy is also recommended, if necessary. In patients with respiratory failure, particularly those with markedly increased CRP level or hypoalbuminemia, intensive and supportive treatments for the respiratory system and the entire body are indispensable.

There remain some issues to be elucidated. The incidence of leflunomide-induced lung injury, at least that of severe one, differs between Japan and Western countries. The high incidences of lung injury and severe lung injury in Japan may be explained by that leflunomide would have been preferably prescribed to patients with preexisting lung disease for a while at the beginning of PMS in Japan, that the prescription might be overdosed for Japanese patients having smaller body weight than those of Western countries, and that major concern might be a genetic difference between Japanese and Western patients.

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