Concise Report

Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis

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Objectives. The possible link between LEF and interstitial lung disease (ILD) has evoked increasing concern. The aim of the present study was to elucidate the prevalence and risk factors for newly developed and/or exacerbated ILD, based on post-marketing surveillance data, in which all RA patients receiving LEF were pre-registered and monitored for 24 weeks in Japan.

Methods. We analysed data from a cohort of 5054 RA patients who were prescribed LEF since its launch in September 2003 in Japan. Multivariable logistic analysis was performed to identify the risk factors for newly developed and/or exacerbation of ILD.

Results. Sixty-one (1.2%) of 5054 RA patients who received LEF were reported to have development and/or exacerbation of ILD as an adverse drug reaction to LEF, judged by the attending physicians. Multivariable logistic regression analysis identified pre-existing ILD (odds ratio (OR) 8.17; 95% CI 4.63, 14.4), cigarette smoking (3.12; 95% CI 1.73, 5.60), a low body weight (<40 kg vs >50 kg) (2.91; 95% CI 1.15, 7.37) and the use of a loading dose (3.97; 95% CI 1.22, 12.9) as independent risk factors for LEF-induced ILD.

Conclusions. Pre-existing ILD was the most important risk factor for LEF-induced ILD. We suggest that LEF should not be prescribed for RA patients complicated with ILD.

KEY WORDS: Leflunomide, Adverse drug reaction, Interstitial lung disease, Rheumatoid arthritis, Risk factor, Smoking, Loading dose.

Introduction

LEF was put on the market in September 2003 as a promising DMARD in Japan, and was demonstrated to retard radiographic progression, as well as improve signs and symptoms of RA [1, 2]. In order to monitor adverse drug reactions including liver dysfunction, haematological disorders and severe skin reactions, which can be observed only in a large and varied population, a post-marketing surveillance programme was conducted in which all RA patients receiving LEF were pre-registered and monitored for 24 weeks.

When LEF was introduced in Japan, interstitial lung disease (ILD) was rarely recognized as an LEF-related adverse event in Western countries in randomized clinical trials or voluntary reporting systems [3-5]. However, post-marketing surveillance revealed that, during the first few months after its introduction in Japan, 16 patients developed de novo or exacerbated ILD, nine of whom died, which raised serious concerns [6]. The causality assessment between LEF use and the reported ILD appeared to be confounded by pre-existing ILD. Thus, a safety information notice was issued on 27 January 2004 regarding the pulmonary toxicity associated with LEF, especially in individuals with coexistent ILD. Subsequently, there were several case reports describing the development of ILD in RA patients receiving LEF [7-12]. Recently, Ju et al. [13] identified 10 cases with LEF-induced ILD out of 1010 Korean RA patients who had been treated with LEF, and demonstrated a significant association between pre-existing lung disease (ILD, old tuberculosis or emphysema) and LEF-induced ILD. Regarding the risk factors, Suissa et al. [14] also reported an increased risk of ILD related to the use of LEF based on a large cohort study, and revealed that patients at high risk of developing LEF-induced ILD were those with a history of MTX use or pre-existing ILD.

The purpose of the present study was to identify the risk factors for LEF-induced ILD by multivariate logistic analysis using data from post-marketing surveillance conducted in Japan. Based on the data obtained, we discuss the appropriate usage of LEF in the treatment of RA.

Patients and methods

Post-marketing surveillance and enrolled patients

The standard dosage and administration of LEF approved in Japan involves starting with a loading dose of 100 mg daily for 3 days, followed by a maintenance dose of 20 mg daily. The daily dose can be reduced to 10 mg for improved tolerability, considering the patient's symptoms or body weight. Since LEF was put on the market in September 2003, all RA patients starting LEF therapy were pre-registered for the post-marketing surveillance programme, which was carried out by Sanofi-Aventis Japan (formerly Aventis Pharma Japan), and were monitored for 24 weeks to assess its efficacy and adverse drug reactions. On 27 January 2004, a safety information notice regarding the relationship between pre-existing ILD and the development of LEF-induced ILD was issued by Sanofi-Aventis Japan. On 22 July 2004, ILD was included as an important component of post-marketing surveillance to circumvent LEF prescription for RA patients with pre-existing ILD. RA patients who were prescribed LEF were thus divided into three cohorts: those who started LEF by 27 January 2004 (Cohort A); those who were prescribed it between January 27 and July 22 (Cohort B); and those who were prescribed LEF between July 23 and September 22 (Cohort C).
prescribed it after 22 July 2004 (Cohort B). The Study Committee for Leflunomide-induced Lung Injury was organized by the Japan College of Rheumatology, and we analysed data from a cohort of 5054 patients with RA who were prescribed LEF, including 3414 patients in Cohort A, 848 patients in Cohort B and 792 patients in Cohort B. The recovery rates of case report forms from the attending doctors in Cohorts A, B and B were 94.4, 86.1 and 56.9%, respectively. LEF-induced ILD as an adverse drug reaction in post-marketing surveillance was judged and reported by attending physicians with their assessment of causality.

Statistical analysis

Before multivariate logistic regression analysis, the explanatory variables (gender, age, body weight, Steinbrocker’s stage and class, disease duration, past history, complications, liver function test abnormalities, renal impairment, smoking, allergy predisposition, past history of drug-related adverse reactions, loading dose, anti-rheumatic drugs used 1 month prior to LEF prescription and anti-rheumatic drugs used in combination with LEF) were tested regarding their association with LEF-induced ILD by univariate analyses with Fisher’s exact test and correlation analyses between each variable. Among the variables that were significant by univariate analysis, age, gender, body weight, pre-existing ILD, smoking and loading dose usage were selected and further analysed by multivariate logistic regression analysis. Body weight and age were classified into three categories [body weight: <40 kg, 40–50 kg and >50 kg (used as a reference); age: <60 years (reference), 60–70 years and >70 years]. A manual step-wise procedure was used, and variables that were significantly associated with LEF-induced ILD underwent multivariate logistic regression analysis to determine the best model. All significance levels were set at $P < 0.05$.

Results

Risk factors for LEF-induced ILD

Among a cohort of 5054 RA patients who were prescribed LEF, 61 (1.2%) were reported to have developed ILD as an adverse reaction of LEF by their physicians in post-marketing surveillance. In terms of the clinical background, RA patients analysed in the present study could be divided into three cohorts (Cohorts A, B and B), depending on the date when they started LEF.

The proportion of RA patients complicated with pre-existing ILD was high (14.7%) in Cohort A. After the safety information notice regarding the possible relationship between pre-existing ILD and LEF-induced ILD was issued, the prescription of LEF was avoided in RA patients complicated with ILD (Cohort B: 2.8%; Cohort B: 0.4%). Although the initial loading dose was not mentioned in the safety information notice, the frequency of loading dose usage also decreased (Cohort A: 85.1%; Cohort B: 57.7%; Cohort B: 39.3%). As shown in Fig. 1, the incidence of LEF-induced ILD decreased after safety information was issued, which coincided with a decrease in the frequency of pre-existing ILD and the use of a loading dose. Among RA patients without pre-existing ILD in all cohorts, 0.7% developed LEF-induced ILD (Table 1).

To identify the risk factors for LEF-induced ILD, multivariate logistic analysis was performed. Among the variables that were significant by univariate analysis, gender, age, body weight, pre-existing ILD, smoking and the initial use of a loading dose were further analysed for multiple logistic regression analysis. As shown in Table 1, pre-existing ILD was the most important risk factor for LEF-induced ILD, with an odds ratio (OR) of 8.17. Smoking, a low body weight (<40 kg vs >50 kg) and loading dose usage were identified as independent risk factors for LEF-induced ILD.

### TABLE 1. Risk factors of LEF-induced ILD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient number</th>
<th>ILD number (%)</th>
<th>Univariate Fisher’s test $P$-value</th>
<th>Multivariate OR (95% CI) $P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>4071</td>
<td>35 (0.9)</td>
<td>-0.0001</td>
<td>0.751 (0.372, 1.519) 0.4260</td>
</tr>
<tr>
<td>Male</td>
<td>983</td>
<td>26 (2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>2624</td>
<td>13 (0.5)</td>
<td>-0.0001</td>
<td>0.0353</td>
</tr>
<tr>
<td>60–70</td>
<td>1610</td>
<td>28 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>812</td>
<td>19 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>2488</td>
<td>37 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–50</td>
<td>1315</td>
<td>12 (0.9)</td>
<td>0.0353</td>
<td>3.115 (1.734, 5.597) 0.001</td>
</tr>
<tr>
<td>&gt;50</td>
<td>191</td>
<td>6 (3.1)</td>
<td>0.0353</td>
<td>3.115 (1.734, 5.597) 0.001</td>
</tr>
<tr>
<td>Pre-existing ILD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−)</td>
<td>4300</td>
<td>28 (0.7)</td>
<td>-0.0001</td>
<td>8.168 (4.630, 14.41) &lt;0.0001</td>
</tr>
<tr>
<td>(+)</td>
<td>562</td>
<td>32 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−)</td>
<td>3669</td>
<td>35 (1.0)</td>
<td>-0.0001</td>
<td>3.115 (1.734, 5.597) 0.001</td>
</tr>
<tr>
<td>(+)</td>
<td>792</td>
<td>23 (3.1)</td>
<td>-0.0001</td>
<td>3.115 (1.734, 5.597) 0.001</td>
</tr>
<tr>
<td>Loading dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−)</td>
<td>1348</td>
<td>7 (0.5)</td>
<td>0.0053</td>
<td>3.966 (1.217, 12.92) 0.0223</td>
</tr>
<tr>
<td>(+)</td>
<td>3706</td>
<td>54 (1.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIG. 1. The incidence of LEF-induced ILD. The incidence of LEF-induced ILD among RA patients prescribed LEF before 27 January 2004, when the alert for LEF-induced ILD was issued (Cohort A) is shown (A). The incidence of LEF-induced ILD among RA patients prescribed LEF between after January 27 (Cohorts B and B) is shown (B). Column 1: overall incidence of LEF-induced ILD; Column 2: incidence of LEF-induced ILD in RA patients without pre-existing ILD; Column 3: incidence of LEF-induced ILD in RA patients with pre-existing ILD. Percentages are displayed at the top of each column.
LEF-induced ILD has been reported with increasing frequency, and several risk factors have been postulated, such as previous or concomitant lung diseases, including pre-existing ILD and a prior usage of MTX or bucillamine [13, 14]. In the present study, we identified pre-existing ILD, cigarette smoking, a low body weight and the initial usage of a loading dose as independent risk factors for LEF-induced ILD, based on data from a large cohort in Japan. The most important risk factor for LEF-induced ILD was pre-existing ILD, with an OR of 8.17, confirming the results of a previous population-based study demonstrating that the causal link between LEF use and the subsequent development of ILD was influenced by pre-existing ILD [14]. The incidence of LEF-induced ILD decreased in Cohorts B and B, coinciding with a decrease in the frequency of pre-existing ILD, indicating that the issuing of a safety notice was effective for reducing LEF-induced ILD.

LEF-induced ILD was observed in 1.2% of RA patients receiving LEF in the present study, which was higher than that estimated (~0.02%) in Western countries [6]. Notably, the frequency of RA patients with pre-existing ILD was high in the present study (14.7% in Cohort A). The reportedly rare incidence of LEF-induced ILD may have resulted in the channelling of RA patients at high risk for LEF-induced ILD (i.e. pre-existing ILD) for adenovirus events. A limitation of the present study was that LEF-induced ILD was not pre-defined in post-marketing surveillance. Thus, after a committee review of 42 cases whose chest X-rays or CT films were accessible to the committee members, two-thirds were considered to be LEF-induced ILD. Another limitation was the lack of background data regarding the frequency of de novo or acute exacerbation of RA-associated ILD (RA-ILD) in Japan. However, the acute exacerbation of RA-ILD is quite rare, despite a relatively high prevalence of asymptomatic ILD in RA. In fact, Mori et al. [15] recently evaluated high-resolution CT (HRCT) findings from a total of 126 Japanese patients with early and long-standing RA in a prospective and consecutive manner, which identified 15 patients (11.9%) with the interstitial pattern and 10 patients (7.9%) with the bronchiolitis pattern. They demonstrated that none of the 15 RA patients with the interstitial pattern presented with acute exacerbation during a follow-up period of 6 months through 4 years. In contrast, we observed that 32 out of 562 RA patients with pre-existing ILD receiving LEF (5.7%) experienced an exacerbation of ILD during a period of 6 months, suggesting that LEF was involved in the acute exacerbation of pre-existing ILD in Japanese patients.

In addition, an initial loading dose of LEF was usually given at its launch in Japan, which may have further increased the risk. Thus, it is considered that avoiding LEF prescription for RA patients with pre-existing ILD, together with the tendency to skip the initial loading dose in Cohorts B and B, led to the decreased incidence of LEF-induced ILD. However, it should also be noted that 0.7% of the RA patients without pre-existing ILD still developed LEF-induced ILD. The prevalence of LEF-induced ILD in Korea (1.0%) reported by Ju et al. [13] is considered to be higher than that in Western countries. The reasons for this difference in the incidence of LEF-induced ILD remain unclear. Previous studies have suggested a possible genetic predisposition to sporadic and familial interstitial pneumonitis [16]. Although genetic polymorphism associated with RA-ILD remains to be elucidated, there may be polymorphism common to RA-ILD and LEF-induced ILD in the Japanese population. Since RA-ILD is seen both in Asia and in Western countries, genetic factors responsible for RA-ILD may be different among ethnic groups. In this case, the predominance of LEF-induced ILD in Japan may be explained by the difference in susceptibility and their distribution of allele frequencies between Japan and other countries. Further investigations are needed to elucidate the polymorphism responsible for RA-ILD among various races and its contribution to the development of LEF-induced ILD.

The mechanism of pre-existing ILD, which predisposes RA patients to LEF-induced ILD, is unknown. One hypothesis is that a common genetic or environmental factor may exist between RA-ILD and LEF-induced ILD. Regarding other risk factors, cigarette smoking may be associated with the exposure of the respiratory tract to potentially hazardous material contained in cigarette smoke and contribute to the pathogenesis of LEF-induced lung injury [17]. Old age was not identified as a risk factor on multivariate logistic analysis. However, age-related pharmacokinetic changes are reportedly associated with various drug toxicities [18]. Therefore, we consider that adverse drug reactions, including ILD, should be monitored cautiously in elderly RA patients. LEF-induced ILD was observed more frequently in RA patients with a low body weight (<40 kg) and in those who were treated with an initial loading dose of LEF. Although we do not have definite data concerning the relationship between blood concentrations of A771726 and the development of LEF-induced ILD, we consider that it might be prudent to avoid the loading dose and start LEF at lower doses in Japanese patients with RA. Since the active metabolite of LEF (A771726) has a long half-life, LEF-induced ILD should still be suspected in RA patients with respiratory distress even after the cessation of LEF [19].

In summary, we identified risk factors for LEF-induced ILD, including pre-existing ILD, cigarette smoking, a low body weight and the use of a loading dose. Since LEF-induced ILD can be life-threatening, we suggest that LEF should not be prescribed to RA patients with concomitant ILD. Another reason to avoid LEF in these patients is that they may have a poor lung reserve and are at risk for respiratory failure in the event of LEF-induced lung injuries. Since the loading dose and a low body weight were identified as risk factors, it might be better to avoid a loading dose and initiate LEF at a lower dose. Patients receiving LEF should be informed of the risk of lung injury and instructed to promptly report respiratory symptoms such as cough, dyspnoea and fever to their physicians.

Discussion

Rheumatology key messages

- Sixty-one of the 5054 RA patients who received LEF developed de novo or exacerbated ILD.
- Pre-existing ILD was the most important risk factor for LEF-induced ILD.

Disclosure statement: T. Takeuchi has received honoraria from Sanofi-Aventis K. K. All other authors have declared no conflicts of interest.

References
