Mod Rheumatol (2008) 18:96–99
DOI 10.1007/s10165-007-0014-z

CASE REPORT

Leflunomide-induced lung injury that developed after its withdrawal, coinciding with peripheral blood lymphocyte count decrease

Takeshi Otsuka · Takako Koyama · Ryoko Ohtani · Hiroaki Niiro · Seiji Yoshizawa · Mine Harada · Shigeko Inokuma

Received: 13 November 2006 / Accepted: 26 September 2007 / Published online: 27 December 2007

Abstract A 60-year-old rheumatoid arthritis (RA) female with lung fibrosis was treated with leflunomide (LEF) for only 12 days, and responded well. Twenty-five days after the withdrawal of the drug, she had fever, dyspnea, and an elevated serum C-reactive protein level. Chest CT revealed ground-glass opacities (GGOs) and consolidations forming a mosaic pattern, in lung fields including the upper, anterior and central areas, and honeycomb patterns in the lung bases and backs. The level of plasma A771726, an active metabolite of LEF, was still as high as that usually noted under LEF therapy. After pulsed steroid and cholestyramine administration, A771726 was depleted and she recovered. The peripheral blood lymphocyte count that had been approximately 1,000/μL, decreased to 220/μL just at the onset of lung injury, and rapidly and steadily returned to the preinjury level preceding recovery from the injury. Serum albumin level decreased in association with lung injury, and gradually returned to the preinjury level. Special caution is necessary when prescribing leflunomide to elderly patients with preexisting interstitial lung disease, and remains necessary until at least 1 month after its withdrawal.

T. Otsuka · T. Koyama · R. Ohtani · H. Niiro · M. Harada
Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

T. Otsuka (✉) · S. Yoshizawa
Department of Internal Medicine,
Munakata Medical Association Hospital, 5-5-3 Taguma,
Munakata 811-3431, Japan
e-mail: tootsuka@munakata-med-hp.gr.jp

S. Inokuma
Department of Allergy and Immunological Diseases,
Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Keywords Leflunomide · Rheumatoid arthritis · Drug-induced interstitial pneumonitis

Introduction

Recent progress in the development of disease-modifying anti-rheumatic drugs (DMARDs) has greatly improved the status of rheumatoid arthritis (RA) patients. However, adverse reactions to DMARDs, including cytopenia and lung injury, are potentially life-threatening [1, 2]. Leflunomide (LEF), which has been available in Japan since September, 2003, is now recognized as one DMARD that occasionally induces interstitial pneumonia [3–6], and fatal outcomes of it in several patients were reported during postmarketing surveillance in Japan [7]. One characteristic distinguishing LEF from other DMARDs is that its biological half-life is as long as 2 weeks, because half of its active metabolite are excreted into the bile canal.

We treated an RA patient who developed serious lung injury more than 3 weeks after stopping LEF administration. Unique XP/CT profiles and a concurrent peripheral blood lymphocyte count change were observed. This patient showed characteristics of LEF-induced lung injury, in terms of background risk factors, developmental fashion, clinical and laboratory features, and predictors for recovery.

Case report

A 60-year-old female with eight-year history of RA was admitted to our hospital because of dyspnea, a cough and a fever. She had once been suspected as having mixed connective tissue disease. In 1999, she was diagnosed as having RA, based on polyarthritis with morning stiffness

and positive rheumatoid factor. Her chest CT revealed a honeycomb pattern, but the patient had no respiratory complaints. Conventional DMARDs including bucillamine, salazosulfapyridine and tiopronin had failed to work well. On January 15, 2004, LEF administration was started at a loading dose of 100 mg/day for three consecutive days; after that, 10 mg/day was the maintenance dose. It had elicited a good response with a decrease in serum CRP level from 3.1 to 1.0 mg/dL. However, LEF was withdrawn because of a fear of lung injury, that was just urgently announced in a press conference. The duration of LEF use was 12 days in total. After discussion with the patient, cholestyramine was not started for the depletion of A771726, since she had better RA symptoms without any adverse effects. On February 20, 25 days after the withdrawal, fever arose, and a cough developed and worsened. Because a chest CT image taken on February 23 showed interstitial pneumonia, the patient was admitted to the attending hospital. The fever subsided once for a day, but recurred to higher than 39°C and dyspnea developed and worsened. She was then transferred to our hospital on February 25. She had no smoking history.

Upon admission, she was 148 cm tall, weighed 39.8 kg, had a fever of 39.3°C, a pulse rate of 102/min, and a blood pressure of 134/66 mmHg. A fine crackle rale was audible bilaterally from the middle to lower lung fields.

The white blood cell count was 7,800/μL, the neutrophil count was 7,371/μL, the lymphocyte count was 273/μL (220/μL, 2 days before admission), platelet count was 18.3×10^4/μL, and the hemoglobin level was 11.6 g/dL. The serum total protein level was 5.5 g/dL, albumin level was 3.0 g/dL (2.7 g/dL, 4 days after admission), the creatinine level was 0.5 mg/dL, and the lactate dehydrogenase level was 335 U/L. The serum CRP level was 11.7 mg/dL, and the immunoglobulin G, A and M levels were 979, 414 and 51 mg/dL, respectively. CRP level increased to 21.9 mg/dL on day 2. Serum KL-6 level, which was 300 U/mL before the start of LEF administration, increased to 600 U/mL. Laboratory tests showed negativity for serum β-D-glucan, cytomegalovirus (CMV)-antigenemia and plasma endotoxin. The plasma A771726 level was 4.2 μg/mL. The creatinine clearance level was 84 mL/min. The time courses of CRP and albumin levels and lymphocyte count are shown in Figs. 1 and 2. Serum rheumatoid factor level, which had been 338 U/mL immediately before the start of LEF administration, continued to decrease (Fig. 1).

Arterial blood gas analysis showed a PaO_2 of 119 Torr and a $PaCO_2$ of 37 Torr, under maximum oxygen inhalation.

Plain chest XP showed ground-glass opacities (GGOs) in the bilateral upper to lower lung fields, with reticular shadows in the costophrenic and supraphrenic peripheries. CT images taken on February 23 in the attending hospital showed mottled GGOs in the lung fields including upper and anterior areas, in addition to honeycomb patterns distributed in the lung bases and backs. CT images taken on February 25 in our hospital showed enhanced GGOs and consolidations distributed bilaterally from the upper to lower lung fields, particularly involving upper to middle, anterior, and central fields (Fig. 2). GGOs/consolidations showed a mosaic pattern, with dense interlobular septa. A little pleural effusion was noted.

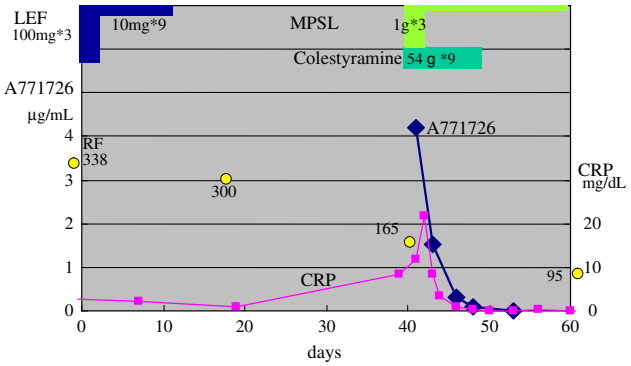

Fig. 1 LEF administration, therapy for lung injury, level of plasma A771726, and serum levels of CRP and rheumatoid factor. The x-axis indicates days after LEF administration. *Asterisk* shows consecutive days of administration. *MPSL* methylprednisolone; *PSL* prednisolone, and *RF* rheumatoid factor

Pulsed intravenous 1,000 mg of methylprednisolone was administered for three consecutive days, and 40 mg of prednisolone followed. Eighteen grams of cholestyramine was orally administered for 11 days. Fever subsided, dyspnea gradually became mild, and oxygen inhalation was tapered and stopped on day 11. The CRP level was 0.3 mg/dL on day 7. Plasma A771726 level decreased to 1.6 μg/mL at day 3, and was lower than 0.1 μg/mL at day 10

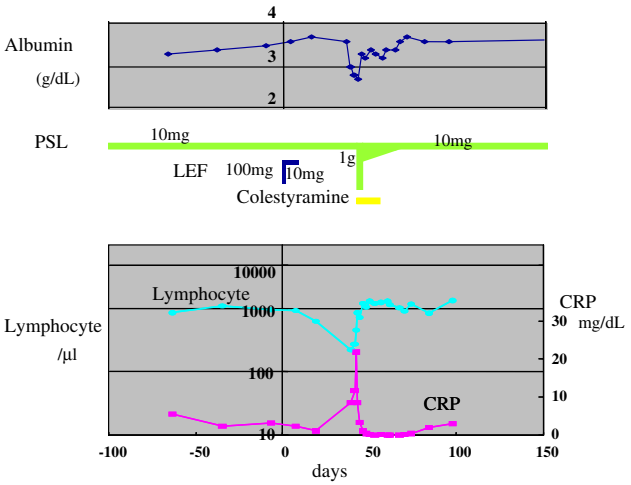

Fig. 2 Time courses of levels of serum CRP and albumin, and of peripheral blood lymphocyte count. The x-axis indicates days after LEF administration

(Fig. 1). The patient was discharged 1 month later, taking daily 20 mg of prednisolone.

Her lungs are still free of GGOs/consolidations, 2 years after discharge; only the preexisting honeycomb pattern remained. Auranofin did not cure her of worsened arthritis under the condition using PSL (10 mg/day). Together with Infliximab, RA patients need to take methotrexate which should be inadequate to use for those having interstitial pneumonia or lung fibrosis. Therefore, Etanercept was introduced and is showing a good effect.

Discussion

LEF is reported to be comparable to methotrexate or sulfasalazopyridine in antirheumatic effect [8, 9]. Its immunomodulating and anti-inflammatory actions are exerted by an active metabolite, A771726, and appear promptly [10–12]. After its introduction in 1998 in US (1999 in EU), major adverse effects including gastrointestinal distress, respiratory infections, and liver disturbance were reported [12]; interstitial pneumonia was rarely noted.

Among the adverse reactions observed in 365 Japanese patients who participated in Phase 1 and Phase II trials, including dose-ranging and long-term studies, an elevated liver enzyme level was slightly more prevalent than in global studies, and none suffered from interstitial pneumonia. At the launch of LEF in September 2003, the Japanese Ministry of Health, Labor and Welfare obliged the pharmaceutical company, Aventis Pharma (now, Sanofi-Aventis) to conduct and sponsor all-case postmarketing surveillance, as a duty for approval. The number of cases to be registered consecutively and surveyed was set to 3,000. Immediately after the launch, lung injury caused by LEF use was noted. On January 27, 2004, when the registrations reached 3,360, 16 patients had developed interstitial pneumonia, and five of them died.

The Japan College of Rheumatology organized the Committee for LEF-Induced Lung Injury, and the efforts by the committee have elucidated that preexisting interstitial pneumonia or fibrosis, and old age are risk factors for the injury, and that peripheral blood lymphocytopenia was one of the features coinciding with the injury onset [7, 13].

Although she had preexisting lung fibrosis, she had been asymptomatic for a long time, and the fibrosis was focally distributed in the peripheries of lower lungs with honeycombs; the upper to middle, anterior, and central fields were not involved. The newly developed abnormalities were GGOs/consolidations throughout the lungs including the upper, anterior and central fields. After recovery, despite their severe involvement, no additional reticulations or honeycombs were remained. In addition, an acute exacerbation of RA lung fibrosis is usually rare. Thus, the acute lung injury developed in this patient could be considered as LEF-induced. The unique radiographic pattern observed in this case could be one of the characteristics of LEF-induced lung injury.

A superimposed infection involving the bilateral lung diffusely was also not likely. Laboratory tests showed negativity for *Pneumocystis jiroveci* or CMV infection.

Leflunomide was effective for her RA, and effective in decreasing RF level continuously from 338 to 95 U for 2 months, even after termination of administration. However, CRP level, which had once decreased, increased acutely to as high as 21.9 mg/dL, in association with severe dyspnea. An increase in CRP level after arthritis improvement with a fever would imply an LEF-induced adverse reaction.

The acute decrease in serum albumin level might have been caused by its massive infiltration into alveoli, or by wasting complicated with severe respiratory distress.

A unique laboratory finding was the peripheral blood lymphocyte count decrease and increase concurrent with the onset of and recovery from the lung injury. The very low minimum count of 220/μL was noted immediately after the onset, and the count increased day by day steadily and rapidly and returned to the preinjury level, with the recovery from the injury. Ochi S et al. also reported a 69-year-old woman developed IP 3 months after institution of LEF, whose laboratory data showed the peripheral blood lymphocyte count decrease (364/μL) [14]. The decrease and increase in lymphocyte count was reported for methotrexate-induced lung injury in RA, in which CD4 T cells infiltrate into alveoli [15]. The participation of lymphocytes in LEF-induced or DMARD-induced lung injury could be very likely. An acute lymphocyte count decrease could be the key to differentiating LEF-induced lung injury from other lung diseases, and a definite increase could be a predictor of recovery.

A particularly important aspect of this case was that lung injury developed 3 weeks after stopping LEF administration. The level of serum A771726 was still sufficiently high, comparable to those in patients receiving a therapeutic dose. It was eliminated after cholestyramine administration, and was undetectable in plasma within 11 days.

The characteristics of this Japanese patient agreed well with those indicated by the Committee including risk factors of being old and having preexisting interstitial lung diseases [13]. These risk factors for LEF-induced lung injury were much more frequently observed in patients with a poor prognosis [7, 13]. Whether and why Japanese RA patients are prone to develop LEF-induced lung injury needs to be elucidated. In conclusion, LEF should be prescribed with special caution because it can induce life-threatening lung injury, even a month after its withdrawal.

References

1. Nanke Y, Kotake S, Akama H, Tomii M, Kamatani N. Pancytopenia and colitis with Clostridium difficile in a rheumatoid arthritis patient taking methotrexate, antibiotics and non-steroidal anti-inflammatory drugs. Clin Rheumatol 2001;20(1):73–5.
2. Nanke Y, Yamada T, Kamatani N. Asymptomatic interstitial pneumonitis induced by bucillamine in a patient with rheumatoid arthritis. Mod Rheumatol 2005;15(5):381–2.
3. Kamata Y, Nara H, Kamimura T, Haneda K, Iwamoto M, Masuyama J, et al. Rheumatoid arthritis complicated with acute interstitial pneumonia induced by leflunomide as an adverse reaction. Intern Med 2004;43:1201–4.
4. Takeishi M, Akiyama Y, Akiba H, Adachi D, Hirano M, Mimura T. Leflunomide induced acute interstitial pneumonia. J Rheumatol 2005;32:1160–3.
5. Hirabayashi Y, Shimizu H, Kobayashi N, Kudo K. Leflunomide-induced pneumonitis in a patient with rheumatoid arthritis. Intern Med 2006;45:689–91.
6. Vallbracht II, Popper HH, Rieber J, Nowak F, Gallenberger S, Piper B, et al. Lethal pneumonitis under leflunomide therapy. Rheumatology (Oxford) 2005;44:1580–1.
7. Sato T, Sawada T, Inokuma S, Sagawa A, Matsuda T, Otsuka T, et al. Analysis of predictive factors for prognosis in Japanese patients with rheumatoid arthritis complicated with leflunomide-induced lung injury. Proceedings of 50th Annual Meeting of Japanese Society of Rheumatology 2006;16:88.
8. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med 1999;159:2542–50.
9. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 1999;353:259–66.
10. Prakash A, Jarvis B. Leflunomide—a review of its use in active rheumatoid arthritis. Drugs 1999;58:1137–64.
11. Manna SK, Aggarwal BB. Immunosuppressive leflunomide metabolite (A771726) blocks TNF-dependent nuclear factor-kappa B activation and gene expression. J Immunol 1999;162:2095–102.
12. Elkayam O, Yaron I, Shirazi I, Judovitch R, Caspi D, Yaron M. Active leflunomide metabolite inhibits interleukin 1beta, tumour necrosis factor alpha, nitric oxide, and metalloproteinase-3 production in activated human synovial tissue cultures. Ann Rheum Dis 2003;62:440–3.
13. Sawada T, Inokuma S, Sagawa A, Matsuda T, Otsuka T, Saeki Y, et al. Leflunomide-associated interstitial pneumonitis: overview of up-to-date occurrence, and analysis on clinical manifestations. Proceedings of 50th Annual Meeting of Japanese Society of Rheumatology 2006;16:88.
14. Ochi S, Harigai M, Mizoguchi F, Iwai H, Hagiyama H, Oka T, Miyasaka N. Leflunomide-related acute interstitial pneumonia in two patients with rheumatoid arthritis: autopsy findings with a mosaic pattern of acute and organizing diffuse alveolar damage. Mod Rheumatol 2006;16(5):316–20.
15. Inokuma S, Kono H, Kohno Y, Hiramatsu K, Ito K, Shiratori K, et al. Methotrexate-induced lung injury in patients with rheumatoid arthritis occurs with peripheral blood lymphocyte count decrease. Ann Rheum Dis 2006;65:1113–4.