Rheumatoid Arthritis Complicated with Acute Interstitial Pneumonia Induced by Leflunomide as an Adverse Reaction

Yasuyuki KAMATA, Hiroyuki NARA, Takeshi KAMIMURA, Kengo HANEDA,
Masahiro IWAMOTO, Junichi MASUYAMA, Hitoaki OKAZAKI and Seiji MINOTA

Abstract

A 49-year-old Japanese man with rheumatoid arthritis acutely developed a skin eruption and severe non-productive cough seventeen days after the administration of leflunomide. Because all bacteriology findings were negative, steroid pulse-therapy was initiated promptly due to the rapidity of chest X-ray progression and the deterioration of arterial blood oxygen pressure. Although cough was induced by methotrexate, interstitial pneumonia was not detected clinically before leflunomide administration. He finally died of respiratory failure 128 days after the onset of acute interstitial pneumonia. According to the post-market surveillance, as high as ~1.1% of the patients on leflunomide have developed interstitial pneumonia in Japan. It is important to emphasize that acute interstitial pneumonia due to leflunomide is a very severe and potentially fatal side effect.

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Key words: leflunomide, interstitial pneumonia, side-effect, rheumatoid arthritis

Introduction

Leflunomide is a newly developed disease-modifying anti-rheumatic drug, which hit the American and European markets in September 1998 and September 1999, respectively (1). It was finally approved by the Japanese government for the treatment of patients with rheumatoid arthritis in April 2003, 5 years after the United States. As it was approved by bridging successful overseas clinical trials without phase III clinical trials in Japan, the Japanese Ministry of

Health required the pharmaceutical company to collect the data from the first 3,000 patients to be given the drug.

In the post-market surveillance, acute interstitial pneumonia probably due to a side effect of leflunomide was reported and the number of such patients is increasing in Japan. Some such patients had a fatal outcome. Acute interstitial pneumonia induced by leflunomide is very serious and brings about a fatal outcome in about 30%.

For editorial comment, see p 1103.

Case Report

A 49-year-old Japanese male patient developed polyarthritis in February 2003, beginning from his right knee and bilateral wrist joints and it exacerbated to include bilateral ankle joints by July. Morning stiffness lasting more than 1 hour and positive rheumatoid factor in his serum confirmed the diagnosis of rheumatoid arthritis and positive C-reactive protein (CRP) endorsed it. Four mg of methotrexate per week and 4 mg/day of prednisolone were initiated in July. In 2 weeks, the patient experienced non-productive cough and methotrexate was withdrawn. Cough disappeared completely soon after the cessation of methotrexate and his chest X-ray was completely normal at this time. He was placed on 6 mg/day of prednisolone for two months. Because his polyarthritic symptoms were aggravated, leflunomide was prescribed on September 22, 2003. An initial loading dose of 100 mg was given for three days followed by 20 mg/day thereafter.

He developed nausea and diarrhea as well as skin eruption 17 days after leflunomide administration and it was immediately withdrawn. Fourteen days after leflunomide cessation, he suddenly experienced severe non-productive cough along with fever and his chest X-ray showed reticular shadow in

From the Division of Rheumatology and Clinical Immunology, Jichi Medical School, Tochigi

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Reprint requests should be addressed to Dr. Yasuyuki Kamata, the Division of Rheumatology and Clinical Immunology, Jichi Medical School, 3311-1 Yakushiji Minamikawachi-machi, Kawachi-gun, Tochigi 329-0498

Figure 1. Chest X-ray on admission showed reticular shadow in his lower lung fields.

his lower lung fields which had not been detected before (Fig. 1). Oxygen pressure of his arterial blood fell all of a sudden, which necessitated an emergency admission to our hospital.

He was 180 cm tall and weighed 75 kg. His blood pressure and pulse-rate were 140/74 mmHg and 80/min regular, respectively. Anemia and jaundice were not detected. Heart sound was normal without any extra-sounds and murmur. Fine crackles were heard over his entire middle and lower lung fields. No abnormal sign was detected in his abdomen. Neurological examination revealed no abnormal findings. Erythematous eruptions with slight exfoliation were detected on his head, auricles, dorsal aspects of his finger joints and elbows. Bilateral wrist and knee joints were swollen.

Laboratory data at the time of admission were summarized in Table 1. Serum levels of CRP, transaminases, LDH and KL-6 (2) were all elevated. Reticulo-nodular shadow was observed in his lower lung fields of his chest X-ray and computed tomography (CT) showed ground-glass opacity (Figs. 1 and 2). Diffusion capacity was decreased in his respiratory function test. Nothing particular was detected on electrocardiogram, echocardiogram, abdominal echogram, and fiberoptic examinations of his upper and lower gastrointestinal tracts. Bacteriology examinations including β -D-glucan (3) were all negative.

He was diagnosed with acute interstitial pneumonia induced by leflunomide and pulse glucocorticoid therapy was

started with 1 g/day of methylprednisolone for 3 days followed by 60 mg/day of prednisolone. Cyclosporine was added to prednisolone; it induced liver damage and needed to be withdrawn.

Because the serum level of leflunomide was as high as 1.6 μ g/ml on the 5th day of admission (on the 24th day after leflunomide-withdrawal), cholestyramine was administered *per os*. Although the serum level of leflunomide was lowered to 0.08 μ g/ml on the 38th day of the withdrawal, the serum KL-6 level increased from 676 U/ml to 1,330 U/ml and reticulonodular shadow of his chest X-ray and ground-glass opacity in his chest CT deteriorated steadily (Fig. 3). Pulse glucocorticoid therapy was started once again without any beneficial effects. Serum levels of β -D-glucan were measured repeatedly and were found to be abnormally high on the 17th day of admission for the first time and polymerase chain reaction for *Pneumocystis carinii* was also found to be positive. Although sulfamethoxazole-trimethoprim compound was prescribed for treatment of *Pneumocystis carinii* pneumonia, due to adverse reactions to kidney and liver function it was withdrawn. His condition continued to deteriorate. He finally died of respiratory failure 128 days after the onset of acute interstitial pneumonia. The entire clinical course is shown in Fig. 4.

Discussion

His previous chest X-rays taken at the annual check-up did not show any signs indicative of interstitial pneumonia. Cough was induced by methotrexate; interstitial pneumonia was not detected clinically before leflunomide administration. Severe non-productive cough along with fever which appeared immediately after leflunomide administration highly indicated that the cause of his interstitial pneumonia could be an adverse reaction of leflunomide. No evidence of infectious etiology including serum β -D-glucan would endorse the above-mentioned etiopathogenesis.

In this case, interstitial pneumonia continued deteriorating even after the serum concentration of leflunomide was decreased by cholestyramine. All the bacterial examinations including the serum level of β -D-glucan were negative on admission indicating that infectious etiology as an instigating factor for his acute interstitial pneumonia was the least possibility.

Interstitial pneumonia as an adverse reaction of leflunomide is rare and the incidence of such cases is reported to be $\sim 0.02\%$ in Western countries. In both the phase II clinical trial with 256 patients enrolled and the long-term clinical trials with 110 patients, no such cases were reported in Japan. The Japanese government approved the use of leflunomide on the condition that all the patients be registered and any adverse reactions be reported. Therefore, the record in the post-market surveillance in Japan could be higher in accuracy in terms of adverse reactions. According to the website of the company (<http://www.aventis.co.jp/arava/aravad/>), 45 cases ($\sim 1.1\%$) developed acute interstitial pneumonia

Table 1. Laboratory Data on Admission

Features (normal range)	Measured value
White blood cell count (3,500–9,100/ μ l)	6,500
Hemoglobin (11.3–15.2 g/dl)	13.7
Platelets (130,000–369,000/ μ l)	341,000
Total protein (6.9–8.4 g/dl)	6.7
Albumin (3.9–5.1 g/dl)	3.2
Aspartate aminotransferase (11–33 U/l)	36
Alanine aminotransferase (4–30 U/l)	43
Lactate dehydrogenase (215–410 U/l)	320
γ -glutamyl transpeptidase (<45 U/l)	42
Alkaline phosphatase (89–285 U/l)	297
Blood urea nitrogen (8–20 mg/dl)	8
Serum creatinine (0.6–1.2 mg/dl)	0.57
Creatine phosphokinase (19–150 mU/ml)	58
C-reactive protein (<0.06 mg/dl)	4.62
Plasma glucose (70–120 mg/dl)	92
IgG (870–1,700 mg/dl)	1,441
IgA (110–410 mg/dl)	264
IgM (46–260 mg/dl)	142
KL-6 (<500 U/ml)	676
Anti-nuclear antibody (<20x)	160x
Rheumatoid arthritis hemagglutination test (<40x)	80x
Anti-neutrophil cytoplasmic antibody (negative)	negative
Anti-Jo-1 antibody (negative)	negative
Soluble IL-2 receptor (220–530 U/ml)	953
Cytomegalovirus antigenemia (negative)	negative
β -D-glucan (<20 pg/ml)	6.3
Arterial oxygen partial pressure (mmHg)	69.6
Arterial carbon dioxide partial pressure (mmHg)	34
Base excess (mmol/l)	0.1
Alveolar-arterial oxygen difference (mmHg)	37.6

Figure 2. Chest CT on admission showed reticulo-nodular shadow with ground-glass opacity in his lower lung fields.

Figure 3. Chest CT on the 81th day of admission showed reticulo-nodular shadow with remarkable ground-glass opacity in his lower lung fields. There were no signs of infection including β -D-glucan at this time.

Figure 4. Entire clinical course of the patient. Pulse: methylprednisolone 1 g/day for 3 days.

probably related to leflunomide, and 19 died, as of May 6, 2004.

The discrepancy in the incidence of this adverse reaction between Japan and other countries can not be explained to date. Unlike methotrexate, interstitial pneumonia as an adverse reaction of leflunomide was not emphasized because of its low frequency. We did not have a biological agent before leflunomide hit the Japanese market. We might have jumped into leflunomide for the treatment of rheumatoid arthritis patients regardless of the concomitant rheumatoid lung disease. We need to scrutinize all the cases of acute interstitial pneumonia for pre-existing rheumatoid lung disease or other predisposing factors. Although we do not have concrete evi-

dence that leflunomide was the real culprit of the acute interstitial pneumonia and the resultant death, we think it is highly probable.

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