

al has been withheld owing to reports of adverse reactions, has been available through the black market.²

The use of the appetite suppressant phenylpropanolamine has been associated with myocardial infarction in patients with angiographically normal coronary arteries.³ To date, no similar data have been reported with regard to phentermine or sibutramine. We report on two otherwise healthy young women who had myocardial infarction with acute ST-segment elevation associated with the use of phentermine and sibutramine.

Patient 1 was a 35-year-old woman in whom acute ST-segment elevation (Fig. 1A) and hypotension developed after the induction of general anesthesia for liposuction. Cardiac biomarkers were elevated (creatinine kinase level, 445 U per liter; troponin T level, 1.86 μg per liter). Echocardiography revealed septal hypokinesia. The coronary arteries appeared normal on angiography.

The patient reported having had asthma since childhood, with mild, intermittent symptoms while she was using bronchodilators; she reported that she had not used these medications recently. She reported having no other medical illnesses and having received no other medications; she was a nonsmoker. She was overweight (body-mass index [the weight in kilograms divided by the square of the height in meters], 29), and she had undergone two previous liposuction procedures for her abdomen and buttocks. She reported having taken phentermine intermittently in the past and for 3 consecutive days before her admission for this procedure.

Patient 2 was an otherwise healthy 24-year-old woman who presented to the emergency room with severe, recurrent retrosternal chest pains. Electrocardiography showed acute inferior myo-

cardial infarction (Fig. 1B). Peak levels of serum creatine kinase and troponin T were 3450 U per liter and 4.25 μg per liter, respectively. The results of coronary angiography were normal. She had no other medical illnesses, was not taking any medications, and was a nonsmoker. She reported having taken sibutramine for the previous 3 months.

Investigations were pursued to rule out other diagnoses in Patient 1 and Patient 2, including cocaine abuse, viral myocarditis, aortic dissection, hypercoagulable states, and autoimmune vasculitis.⁴ In both patients, electrocardiography showed complete resolution of the ST-segment elevation within 24 hours. The absence of any attendant cardiovascular risk factors and the negative results of other studies led us to conclude that the use of appetite suppressants was responsible for the myocardial infarction in each of the two patients.

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1. Annual report of the Malaysian Adverse Drug Reactions Advisory Committee 2005. Kuala Lumpur, Malaysia: National Pharmaceutical Control Bureau, Ministry of Health, 2005.
2. Dangers of slimming pills. The Professional Bulletin of the National Poison Centre, Malaysia (online). August 2002. (Accessed October 11, 2007, at <http://www.prn2.usm.my/mainsite/bulletin/2002/prn35.html>.)
3. Pilszczek FH, Karcic AA, Freeman I. Dexatrim (phenylpropanolamine) as a cause of myocardial infarction. *Heart Lung* 2003;32:100-4.
4. Chandrasekaran B, Kurbaan AS. Myocardial infarction with angiographically normal coronary arteries. *J R Soc Med* 2002;95:398-400.

Pneumocystis Pneumonia Associated with Infliximab in Japan

TO THE EDITOR: Infliximab, a monoclonal antibody against tumor necrosis factor α (TNF- α), is used in Japan for the treatment of patients with active rheumatoid arthritis that is resistant to methotrexate.¹ Methotrexate is used only for patients who do not have a response to or cannot tolerate other disease-modifying antirheumatic drugs, such as sulfasalazine. Infliximab is not used as primary therapy for rheumatoid arthritis in Japan.

Strict postmarketing surveillance of infliximab

and etanercept, a drug that blocks the action of TNF, revealed incidences of pneumocystis pneumonia in Japanese patients with rheumatoid arthritis that were higher (0.4% and 0.2%, respectively) than those in Western countries.² We therefore conducted a multicenter, case-control study of pneumocystis pneumonia in patients with rheumatoid arthritis who were receiving infliximab therapy.

The study protocol was approved by the insti-

tutional review board at our hospital; informed oral consent was obtained from all patients. Included in the study were patients who met the 1987 American College of Rheumatology criteria for rheumatoid arthritis³ and who were receiving 3 mg of infliximab per kilogram of body weight every 8 weeks with concomitant methotrexate. A total of 21 patients with pneumocystis pneumonia were collected through postmarketing surveillance or voluntary case reports from 14 hospitals. Another 102 patients without pneumocystis pneumonia were selected at random from a consecutive series of patients from three hospitals participating in the study. A diagnosis of pneumocystis pneumonia was definitive if *Pneumocystis jirovecii* was found on microscopical analysis of respiratory samples from patients with clinical manifestations (pyrexia, dry cough, or dyspnea), hypoxemia, and radiologic findings compatible with pneumocystis pneumonia. The diagnosis of pneumocystis pneumonia was presumptive if a patient met all three criteria and had either a positive polymerase-chain-reaction test for *P. jirovecii* DNA or an increased serum level of (1→3) β -D-glucan with an appropriate response to the standard treatments for pneumocystis pneumonia.^{4,5} We did not test for the presence or absence of human immunodeficiency virus.

The diagnosis of pneumocystis pneumonia was definitive in 2 patients and presumptive in 19 patients. As compared with patients who did not have pneumocystis pneumonia, patients with pneumocystis pneumonia were significantly older (median age, 65 years vs. 55 years; $P < 0.001$); had a higher prevalence of coexisting pulmonary disease, including interstitial pneumonia, chronic obstructive pulmonary disease, bronchiectasis, chronic bronchitis, follicular bronchiolitis, and old pulmonary tuberculosis (47.6% vs. 10.8%, $P < 0.001$); and were treated with a higher daily dose of prednisolone (median dose, 7.5 mg vs. 5.0 mg; $P = 0.001$).

Among patients with pneumocystis pneumonia, the hazard ratio for an age of at least 65 years was 3.77 (95% confidence interval [CI], 1.54 to 9.25), the hazard ratio for a daily dose of prednisolone of at least 6 mg was 3.76 (95% CI, 1.37 to 10.3), and the hazard ratio for the presence of coexisting pulmonary disease was 2.54 (95% CI, 1.00 to 6.46). All comparisons were calculated with the use of Cox proportional-hazards regression. The Cox model with age and the use of pred-

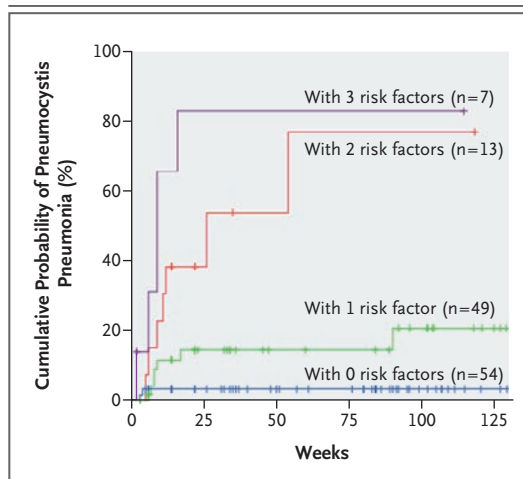


Figure 1. Cumulative Probability of Pneumocystis Pneumonia in Patients with Rheumatoid Arthritis Associated with Infliximab Therapy, According to the Number of Risk Factors.

A total of 123 patients with rheumatoid arthritis were stratified according to the number of risk factors present, including an age of at least 65 years, a daily dose of prednisolone of at least 6 mg, and the presence of coexisting pulmonary disease. The cumulative probability of pneumocystis pneumonia was calculated by means of the Kaplan–Meier method. Patients with two risk factors and those with three risk factors had a significantly higher cumulative probability of pneumocystis pneumonia than did patients with no risk factors ($P < 0.001$ for both comparisons, by the log-rank test) and those with only one risk factor ($P = 0.002$ and $P < 0.001$, respectively). All analyses were performed with the use of SPSS software, version 15.0 (SPSS Japan).

nisolone as continuous variables and coexisting pulmonary disease as a categorical variable provided similar results. Pneumocystis pneumonia developed more frequently in patients with two or three of the risk factors than in the other patients (Fig. 1). More research is needed to determine precisely which patients with rheumatoid arthritis who are receiving infliximab therapy have a risk of pneumocystis pneumonia that is high enough to warrant prophylaxis.

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1. Miyasaka N, Takeuchi T, Eguchi K. Proposed [corrected] Japanese guidelines for the use of infliximab for rheumatoid arthritis. *Mod Rheumatol* 2005;15:4-8. [Erratum, *Mod Rheumatol* 2005;15:322.]
2. Takeuchi T, Tatsuki Y, Nogami Y, et al. Post-marketing sur-

veillance of the safety profile of infliximab in 5,000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* (in press).

3. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
 4. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. *N Engl J Med* 2001;344:168-74.
 5. Yasuoka A, Tachikawa N, Shimada K, Kimura S, Oka S. (1→3) beta-D-glucan as a quantitative serological marker for *Pneumocystis carinii* pneumonia. *Clin Diagn Lab Immunol* 1996;3:197-9.
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