EFV levels ($P = .008$) and NVP dosage ($P < .001$) were independently and positively associated with the steady-state plasma NVP levels in multivariate analysis.

The switch from EFV to NVP can lead to a time-limited subtherapeutic steady-state plasma NVP level. In this context, genetic variability may be responsible for the low steady-state plasma NVP levels among patients with previous low steady-state plasma EFV levels. Although the virologic consequences of a time-limited subtherapeutic steady-state plasma NVP level are unknown, subtherapeutic steady-state plasma NVP levels have been associated with virologic failure after a switch from protease inhibitor–based therapy [6]. To limit exposure to subtherapeutic steady-state plasma NVP levels, we suggest that determining the steady-state plasma EFV level before the switch to NVP may be helpful for deciding whether to start NVP at 200 mg per day (patients with high baseline EFV levels) or 400 mg per day (patients with low baseline EFV levels).

Acknowledgments

Potential conflicts of interest. J.-J.P. reports that he has received recent research funding from Boehringer Ingelheim, Abbott, Gilead, and Bristol-Myers Squibb. All other authors: no conflicts.

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Clinical Infectious Diseases 2010; 50(11):1547–1548

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Risk of Fatal Adverse Events after H1N1 Influenza Vaccination

To the Editor—The safety of the H1N1 influenza vaccine is controversial. Some fatal cases were reported after receipt of H1N1 influenza vaccine. A recent study shows that no patterns in age, sex, or type of underlying medical condition were observed that might lead investigators to suspect a causal link with H1N1 influenza vaccination [1]. However, the situation is different in Japan.

Some patients died immediately after H1N1 influenza vaccination in Japan. Severe adverse events following receipt of H1N1 influenza vaccine may occur in pregnant women, patients with underlying diseases, and young children, who have been preferentially vaccinated since October 2009 in Japan.

We investigated clinical features of patients who died immediately after H1N1 influenza vaccination, using the information on adverse events announced by the Ministry of Health, Labor, and Welfare. Physicians are required to report severe adverse events after H1N1 influenza vaccination to the Ministry of Health, Labor, and Welfare.

From 19 October to 21 December 2009, an estimated 15 million doses of monovalent, inactivated H1N1 influenza vaccine without an adjuvant were distributed in Japan. As of 7 January 2010, 107 fatal cases were reported, including 2 autopsied cases. Of the 107 cases, 98 (91.6%) involved persons aged ≥60 years. All the deceased individuals had underlying diseases, including respiratory disease ($n = 39$), cardiovascular disease ($n = 31$), and neurologic disorders ($n = 19$). Exacerbation of underlying diseases was the ma-
Major cause of death \((n = 22)\). Adverse events immediately after H1N1 influenza vaccination, such as anaphylactic reaction, did not cause any deaths. A total of 34 cases did not show causal relationships between H1N1 influenza vaccination and death, whereas for 73 cases, it was unclear whether there was a causal relationship. Figure 1 shows the distribution of the date of death.

Interestingly, most of the fatal cases occurred within 4 days after H1N1 influenza vaccination. After peaking within 24 h after H1N1 influenza vaccination, the number of fatal cases greatly decreased (Figure 1). These results suggest a strong association between H1N1 influenza vaccination and the patient deaths. If H1N1 influenza vaccination were not associated with the patient deaths, the number of fatal cases might not have peaked shortly after vaccination.

The causal relationship between H1N1 influenza vaccination and most of the fatal cases was unclear. Inflammatory responses caused by H1N1 influenza vaccination might have worsened the underlying diseases, leading to fatal complications.

A randomized, controlled trial should be required for evaluation of the safety of the H1N1 influenza vaccine. However, it is difficult to conduct a randomized, controlled trial, because the government recommends vaccination of individuals with some underlying diseases.

On the other hand, a case-control study, comparing subjects who receive H1N1 influenza vaccine with subjects who do not receive it, is not adequate to evaluate the vaccine’s safety. Because clinicians determine who will be the subjects, selection bias must exist.

The safety of the H1N1 influenza vaccine is generally ensured; however, fatal adverse events may occur in a few patients, especially elderly patients with underlying diseases. Clinicians should recognize the risk of fatal adverse events after H1N1 influenza vaccination.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Clinical Infectious Diseases 2010; 50(11):1548–1549 © 2010 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2010/5011-0025$15.00 DOI: 10.1086/652719