Gastrointestinal Events in High-Dose vs Standard-Dose Influenza Vaccine Recipients

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INTRODUCTION

A high-dose inactivated influenza vaccine (IIV-HD), developed to address the need for improved influenza vaccines in older adults, was licensed for use in the United States in December 2009. IIV-HD contains 4 times the amount of hemagglutinin (HA) antigen of vaccine strain per dose compared with standard-dose inactivated intramuscular influenza vaccines (IIV-SD). Postlicensure safety of IIV-HD was assessed by investigators at the US Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) using the Vaccine Adverse Events Reporting System (VAERS) database during the first year that the vaccine was available for public use (2010–2011 influenza season). In the VAERS study, the investigators found increased reporting of vomiting and concluded that a clinically important imbalance between the reported and expected number of gastrointestinal (GI) events after IIV-HD receipt was possible. They also called for future studies to assess this potential association [1]. Interrogation of the data from a large randomized controlled efficacy trial performed during the 2011–2012 and 2012–2013 Northern Hemisphere influenza seasons [2] provided an opportunity to evaluate the theoretical association between IIV-HD and gastrointestinal events. As the randomized controlled trial only collected safety information related to serious adverse events (SAEs), the present supplementary analysis reported herein does not include nonserious GI events that might have occurred.

METHODS

The original study was a phase IIIb/IV, randomized, double-blind, active-controlled, multicenter trial in adults ≥65 years of age spanning 2 influenza seasons, 2011–2012 and 2012–2013 [2]. Participants were randomized in a 1:1 ratio to receive 1 dose of either IIV-HD (Fluzone High-Dose vaccine, Sanofi Pasteur, Swiftwater, PA) or IIV-SD (Fluzone Vaccine, Sanofi Pasteur, Swiftwater, PA) before the start of the influenza season and were followed until the end of each season. Subjects enrolled in year 1 and who still met eligibility criteria could be re-enrolled and re-randomized in year 2, regardless of whether or not a serious event occurred in year 1.

Data on SAEs were collected from the day of enrollment until the last telephone contact with the subject during each respective study year. SAEs were defined as events leading to death or hospitalization (or its prolongation) that were considered life-threatening or medically important or that resulted in disability [3]. Based on available medical information, study investigators reported the diagnoses associated with all SAEs through an electronic data capture system. All reported SAE diagnostic categories were coded as “preferred terms” using the Medical Dictionary for Regulatory Activities. Two physicians blinded to treatment group independently reviewed all the preferred terms that were used to code all SAEs reported in the study (publicly available at clinical-trials.gov [4]). A total of 1347 SAE preferred terms were reviewed. To capture events similar to those reported in the VAERS study, coded SAEs considered likely to result in symptoms of nausea, vomiting, or diarrhea were selected by each medical reviewer based solely on the medical nature of the reported preferred term for the diagnosis. The physician-reviewers then compared their respective selections and exclusions and reached consensus on the selected terms to be included in the analysis.

Analyses were performed using all participants who received the study vaccine (full analysis set [FAS]) and according to the vaccine that participants actually received. The rates, as defined by events per 1000 subject-seasons, were obtained for each study season and for both seasons combined.

All statistical analyses were performed using SAS Enterprise Guide 5.1 (SAS Institute, Cary, NC).
RESULTS

Of the 31,989 participants enrolled, 15,991 were randomized to IIV-HD and 15,998 were randomized to IIV-SD; 31,989 (99.9%) participants received study vaccine and were included in the FAS (15,992 IIV-HD and 15,991 IIV-SD). There was 1 more participant who received study vaccine and was included in the IIV-HD group than in the IIV-SD group (2.69 events/1000 participant-seasons), for a relative risk of 0.91 (95% confidence interval [CI], 0.59–1.40) (Table 1). Of participants in both groups with selected serious GI events, 54.7% were women, 96.0% were white, and the mean age was 74.4 years. Only 1 event occurred in each group within 7 days of immunization: viral diarrhea in an IIV-HD participant and colitis in an IIV-SD participant. The relative risk of a GI SAE within 7 days of immunization was 1.00 (95% CI, 0.06–15.99). Another 10 events occurred within 30 days after immunization (5 in each group), giving a cumulative relative risk of 1.00 (95% CI, 0.32–3.10) for that time period. In the IIV-HD group, the events included 2 episodes of nausea and diarrhea, 1 episode each of colitis, pancreatitis, acute pancreatitis, and viral diarrhea. In the IIV-SD group, events included 2 episodes of gastroenteritis, 2 episodes of colitis, and 1 episode each of infectious enterocolitis and pancreatitis. The remaining GI episodes occurred more than 30 days after immunization. The median time to onset for symptoms was 98 days from immunization for IIV-HD and 122 days for IIV-SD (P = .318).

Rates of GI SAEs varied somewhat between the 2 study years: during the first study year, 27 events (3.72 events/1000 participant-seasons) were reported in the IIV-HD group and 43 events (2.69 events/1000 participant-seasons) in the IIV-SD group. Approximately the End of Each Influenza Season

Overall, in the course of the study, 103 (0.64%) IIV-HD recipients experienced at least 1 gastrointestinal event (both those considered likely to result in symptoms of nausea, vomiting, or diarrhea and those not), as did 148 (0.93%) IIV-SD recipients [2]. Thirty-nine selected serious GI events possibly associated with nausea, vomiting, or diarrhea occurred in the IIV-HD group (2.44 events/1000 participant-seasons), and 43 events occurred in the IIV-SD group (2.69 events/1000 participant-seasons), for a relative risk of 0.91

| Table 1. Rates of Selected Gastrointestinal Serious Adverse Events During the Entire Surveillance Period (From Vaccination to Approximately the End of Each Influenza Season) |
|-----------------------------------------------|
| **Any selected gastrointestinal events**      | **IIV-HD** | **Year 1** | **(n = 7254), No. (Rate)** | **Year 2** | **(n = 8748), No. (Rate)** | **Combined** | **(n = 15992), No. (Rate)** |
|-----------------------------------------------|------------|------------|----------------------------|------------|----------------------------|-------------|----------------------------|
| Relative Risk [95% CI]                        | 1.00 (0.06–1.96) | 1.00 (0.06–1.96) | 0.91 (0.59–1.40) |
| **Alcoholic pancreatitis**                    | 1 (0.14)   | 1 (0.14)   | 1.00 (0.06–1.96) | 0 (0.00)   | 0 (0.00)   | NA           | 1 (0.06)   | 1 (0.06)   | 1.00 (0.06–1.96) |
| **Colitis**                                   | 2 (0.28)   | 6 (0.83)   | 0.33 (0.07–1.65) | 1 (0.11)   | 1 (0.11)   | 1.00 (0.06–1.96) | 3 (0.19)   | 7 (0.44)   | 0.43 (0.11–1.66) |
| **Diarrhea**                                  | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 2 (0.23)   | NA           | 0 (0.00)   | 2 (0.13)   | NA           |
| **Diarrhea infectious**                       | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           |
| **Enterocolitis infectious**                  | 0 (0.00)   | 1 (0.14)   | NA           | 0 (0.00)   | 1 (0.11)   | NA           | 0 (0.00)   | 2 (0.13)   | NA           |
| **Enterocolitis viral**                       | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           | 1 (0.06)   | 0 (0.00)   | NA           |
| **Gastroenteritis**                           | 5 (0.69)   | 6 (0.83)   | 0.83 (0.25–2.73) | 5 (0.57)   | 9 (1.03)   | 0.56 (0.19–1.66) | 10 (0.63)   | 15 (0.94)   | 0.67 (0.30–1.48) |
| **Gastroenteritis bacterial**                 | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 1 (0.11)   | NA           | 0 (0.00)   | 1 (0.06)   | NA           |
| **Gastroenteritis norovirus**                 | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           |
| **Gastroenteritis viral**                     | 2 (0.28)   | 1 (0.14)   | 2.00 (0.18–22.02) | 2 (0.23)   | 1 (0.11)   | 2.00 (0.18–22.08) | 4 (0.25)   | 2 (0.13)   | 2.00 (0.37–10.92) |
| **Gastrointestinal infection**                | 0 (0.00)   | 1 (0.14)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 1 (0.06)   | NA           |
| **Gastrointestinal viral infection**          | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           |
| **Nausea**                                    | 1 (0.14)   | 0 (0.00)   | NA           | 1 (0.11)   | 0 (0.00)   | NA           | 2 (0.13)   | 0 (0.00)   | NA           |
| **Pancreatitis**                              | 8 (1.10)   | 2 (0.28)   | 3.99 (0.85–18.80) | 1 (0.11)   | 0 (0.00)   | NA           | 9 (0.56)   | 2 (0.13)   | 4.50 (0.97–20.82) |
| **Pancreatitis acute**                       | 3 (0.41)   | 2 (0.28)   | 1.50 (0.25–8.96) | 0 (0.00)   | 5 (0.57)   | NA           | 3 (0.19)   | 7 (0.44)   | 0.43 (0.11–1.66) |
| **Pancreatitis necrotizing**                  | 0 (0.00)   | 0 (0.00)   | NA           | 0 (0.00)   | 1 (0.11)   | NA           | 0 (0.00)   | 1 (0.06)   | NA           |
| **Pancreatitis relapsing**                    | 2 (0.28)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           | 2 (0.13)   | 0 (0.00)   | NA           |
| **Viral diarrhea**                            | 1 (0.14)   | 0 (0.00)   | NA           | 0 (0.00)   | 0 (0.00)   | NA           | 1 (0.06)   | 0 (0.00)   | NA           |
| **Vomiting**                                  | 1 (0.14)   | 1 (0.14)   | 1.00 (0.06–15.96) | 2 (0.23)   | 1 (0.11)   | 2.00 (0.18–22.08) | 3 (0.19)   | 2 (0.13)   | 1.50 (0.25–8.98) |

Abbreviations: CI, confidence interval; IIV-HD, high-dose inactivated influenza vaccine; IIV-SD, standard-dose inactivated influenza vaccine; No., number of events; rate, events per 1000 participant-seasons.
participant seasons) occurred in the IIV-HD group and 21 (2.90 events/1000 participant seasons) occurred in the IIV-SD group, giving a relative risk of 1.28 (95% CI, 0.73–2.27); during the second study year, 12 events (1.37 events/1000 participant seasons) occurred in the IIV-HD group and 22 (2.51 events/1000 participant seasons) occurred in the IIV-SD group, giving a relative risk of 0.55 (95% CI, 0.27–1.10).

**DISCUSSION**

Nausea and vomiting have been reported after administration of inactivated influenza vaccine in adults, but these occur at a frequency similar to that after the administration of placebo [5]. Nausea has been noted with an influenza vaccine of purified hemagglutinin (HA) proteins produced in insect cells, but, as with the previous study, the proportion of affected subjects was similar to those receiving placebo [6]. The biological mechanism of GI side effects after influenza vaccination, if 1 exists, is not clear. Increased cytokine levels postvaccination may elicit a variety of symptoms, including those of the gastrointestinal tract, but this has not been specifically documented with the inactivated influenza vaccines. Two large, retrospective studies have shown increased frequency of gastrointestinal events in children following influenza vaccination [7, 8], and although it was not possible to rule out a vaccine-related reaction, it has been hypothesized that this association may be due to exposure to gastrointestinal infections while at the physician’s office for immunization [7, 8].

VAERS is a national postmarketing safety surveillance program that uses postmarket surveillance of licensed vaccines in the United States. Reporting of adverse events into VAERS allows the CDC and FDA to detect adverse events that may not be identified in prelicensure clinical trials [9]. VAERS uses data to find disproportional reporting of individual adverse events postvaccination. This system is limited, however, by its use of voluntary reporting, passive surveillance, and the inconsistent quality of the data entered. Additionally, this system cannot estimate the level of risk of an event after vaccination. The study based on VAERS reported a higher occurrence of vomiting and nausea in IIV-HD recipients compared with those receiving IIV-SD for both serious and nonserious events. When data mining was performed, the VAERS system contained 99 reports of the preferred term “vomiting.” The majority of events (84%) were considered nonserious, and most of the affected patients (75%) recovered before the submission of the VAERS form [1]. The safety data from the large phase IIIb/IV study that compared IIV-HD with IIV-SD only collected serious adverse events. As such, episodes of nonserious nausea and vomiting were not collected, which may have resulted in underestimation of the total number of nausea and vomiting episodes in our analysis. Reassuringly, neither the VAERS-based study nor the large clinical trial signaled an increase in severe gastrointestinal side effects. This would be relevant if there were a true association between IIV-HD and gastrointestinal events, but this association was undetected in the current study; the association would likely to be restricted to events of limited clinical significance, unlikely to offset the benefits of IIV-HD in the prevention of influenza-related events. The differences in the reporting of serious GI events between the phase IIIb/IV study and the VAERS study could have been due to the different periods in which the studies were conducted, which may have been associated with sporadic outbreaks of GI viral disease. The most likely explanation for the difference between the studies, however, is reporting bias. The advantage of using the clinical trial data to investigate the hypothetical relationship between the IIV-HD and GI side effects is the elimination of reporting bias; participants and investigators were all blinded to which study vaccine was administered. Furthermore, due to the double-blind randomized controlled design of the phase IIIb/IV study, the estimates reported here are expected to be unbiased overall.

This report provides reassurance that IIV- HD is unlikely to be associated with an increased risk of serious GI side effects compared with IIV-SD.

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