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Safety of Zostavax™—A cohort study in a managed care organization

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ABSTRACT

Background: Zostavax™ is a live, attenuated varicella-zoster virus vaccine indicated for the prevention of herpes zoster (shingles). An observational post-licensure (Phase IV) study was conducted at Kaiser Permanente Northern California (KPNC), a US managed care organization, to assess the safety of zoster vaccine in people 60 years of age or older, vaccinated in routine medical care.
Methods: We performed a cohort study, comparing rates of clinical events resulting in hospitalizations or emergency department visits in a 42-day risk time period immediately following vaccination with rates in the same cohort in a subsequent comparison time period. The study data were reviewed and interpreted by an external safety review committee of 3 independent experts.
Results: Approximately 29,000 people ≥ 60 years of age were vaccinated with zoster vaccine from July 2006 to November 2007. Of the 386 comparisons performed for the main analysis, 4 had an increased relative risk with a nominal p-value ≤ 0.05. After medical records review, the timing of these conditions and procedures was found to be often prior to vaccination, and no clear increase in health events was observed in the risk period following vaccination compared to later. Persons receiving zoster vaccine appeared to be in their optimal health at the time of vaccination, which led to an apparent protective effect of the vaccine for some health outcomes, due to the study design.
Conclusions: There was no evidence of a safety concern for zoster vaccine.
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1. Introduction

Herpes zoster (HZ), commonly known as shingles, is a painful viral exanthem caused by reactivation of varicella-zoster virus (VZV) from a latent infection of dorsal sensory or cranial nerve ganglia. The likelihood of contracting HZ increases with age and the lifetime risk of HZ approximates 30% [1–4]. Rates of HZ appear to be increasing over the last several decades [2,3,5,6], but the reasons for this are unclear [7,8].

In May 2006, the frozen formulation of Zostavax™ (zoster vaccine live) was approved in the United States (U.S.) for the prevention of HZ in people 60 years of age or older. A refrigerated formulation was subsequently approved. Zoster vaccine is a single-dose, sterile, preservative-free, live attenuated VZV vaccine that is administered via subcutaneous injection. When reconstituted, each 0.65-mL dose contains a minimum of 19,400 plaque-forming units (PFU) of the Oka/Merck strain of VZV. This is the same strain as in the varicella vaccine for children, but with a higher potency.

In clinical development, zoster vaccine demonstrated an excellent safety profile. As of the end of 2011, vaccine safety was evaluated in a total of approximately 55,000 adult recipients in pre- and post-licensure clinical trials. In the Shingles Prevention Study (SPS) [9,10], a placebo-controlled efficacy trial (19,270 zoster vaccine and 19,276 placebo recipients), the number and types of serious adverse events (SAE) were similar in the two groups. Reactions at the injection site were more frequent among vaccine recipients but were generally mild [9]. In a recent trial among over 22,000 subjects 50–59 years of age [11] (11,211 zoster vaccine and 11,228 placebo recipients), no differences were observed in SAEs reported over 6 months post vaccination between the zoster vaccine and placebo recipients (2.1% vs. 1.9% respectively) nor in the 42 days post vaccination. In a post-licensure safety trial of ~6000 zoster vaccine and ~6000 placebo recipients 60 years of age or older, the risk of SAE was similar between the two study groups both during the 1–42 days and the 6 months post vaccination [12]. Another large post-licensure study, using data from the Centers for Disease Control and Prevention (CDC)'s Vaccine Safety Datalink (VSD) also found zoster vaccine to be safe and well-tolerated [13,14].

This cohort study was initiated in January 2007 as a post-licensure commitment to the U.S. Food and Drug Administration

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(FDA) to assess the general safety of zoster vaccine in a target population of 20,000 subjects 60 years of age or older, vaccinated during routine medical care.

2. Methods

2.1. Study setting

This retrospective cohort study was conducted at Kaiser Permanente Northern California (KPNC), an integrated health care system that provides comprehensive health services for over three million residents of Northern California. KPNC members are ethnically diverse and similar to the population of California in terms of age, but somewhat under-representative of the low income population [13–15]. Each KPNC member has a unique medical record number which links information across services for the same individual over time. KPNC maintains computerized records for all outpatient clinic visits, emergency department (ED) visits, and hospitalizations. These records include diagnoses, laboratory tests, medications, and procedures, as well as demographic and membership information. Over 90% of hospitalizations and ED visits for KPNC members occur within the KPNC system, and medical encounters occurring outside of KPNC are captured through databases tracking referrals and claims for reimbursement. Death is identified if it occurs within the KPNC system or if membership is terminated by the member's family because of death. KPNC can also link membership files to California mortality data to ascertain death, but with a one- to two-year delay. In addition, KPNC maintains registries of members with specific underlying diagnoses, including diabetes mellitus and chronic obstructive pulmonary disease (COPD).

Detailed vaccination data are tracked and captured by the Kaiser Immunization Tracking System (KITS), one of the largest electronic tracking systems for immunization in the U.S. The KITS system collects, among other information, the patient's medical record number, date of vaccination, type of vaccine, route of administration, facility in which the vaccine was administered, manufacturer and vaccine lot number, and can be linked to other data sources to get additional information. Although zoster vaccine was provided conveniently and at no additional cost to KPNC members, making it likely that most vaccines were received within the system, it is possible that some vaccines were received at other health facilities. In case, the only way we would have captured the data is if they reported the vaccine to their KPNC provider, and it was recorded in KITS.

The study was reviewed and approved by the KPNC Institutional Review Board.

2.2. Study population and design

KPNC members 60 years of age or older vaccinated with zoster vaccine from July 2006 through November 2007 were eligible to be included in the study. To ensure complete follow-up, especially of care received at non-KPNC facilities, study subjects were required to have continuous KPNC membership for at least 180 days (6 months) after vaccination with zoster vaccine. However, monitoring of possible deaths was performed in all vaccinated subjects postvaccination.

Subjects were followed for all postvaccination hospitalization and ED visits identified by International Classification of Diseases and Related Health Problems-9 (ICD-9) codes in the electronic medical records. The rate of all diagnosis codes and some pre-specified procedure codes of interest listed for hospitalizations and ED visits occurring in a 42-day risk period (days 1–42) following vaccination with zoster vaccine was compared to that in a 90-day postvaccination comparison period (days 91–180 post vaccination), using vaccinees as their own "controls" (Fig. 1). The 42-day risk interval was based on earlier safety studies conducted on zoster vaccine [9,10]. All hospitalization and ED visit codes were counted, irrespective of whether they corresponded to new or pre-existing conditions.

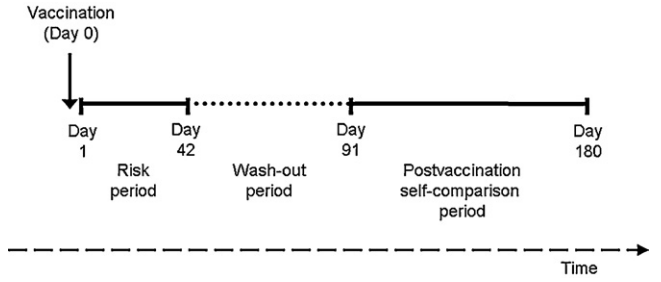

Fig. 1. Study risk period and postvaccination comparison period (subjects vaccinated July 2006–November 2007).

2.3. Code grouping of health outcomes

Diagnosis and procedure codes were grouped into clinically meaningful health outcome (HO) categories using the hierarchical classification of ICD-9 codes developed by the Healthcare Cost and Utilization Project (HCUP) (Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). The HCUP grouping is structured into 18 high level diagnosis categories and 16 high level procedure categories. In this study, all HCUP high level diagnosis categories were kept for use in the study analysis, except a category of miscellaneous codes (i.e., diagnosis category 18, which contains all residual, unclassified, and E codes. Although prior studies had not shown an increased risk in cardiovascular conditions, because it was known that varicella virus can associated with vasculitis [16] and myocarditis [17], special attention was devoted to cardiovascular outcomes as well. Before any data analysis, 5 HCUP procedure sub-categories related to the cardiovascular system (procedure category 7) were selected by the study safety review committee (SRC, see the SRC section below) for inclusion into the analysis. These procedures were 7.1 – Heart valve procedures; 7.2 – Coronary artery bypass graft; 7.3 – Percutaneous transluminal coronary angioplasty (PTCA); 7.4 – Coronary thrombolysis; and 7.5 – Diagnostic cardiac catheterization.

2.4. The safety review committee (SRC)

The study methods and data were reviewed by the SRC, an independent scientific committee in charge of scientific oversight of the study. The SRC was composed of three experts: a vaccine safety specialist, a geriatrician, and a pharmacoepidemiologist, who worked in collaboration with the research team. The SRC reviewed and provided input on the study methods, reviewed general safety data, and requested additional ad-hoc analyses or medical record reviews to assist with evaluation of the safety data.

2.5. Statistical analysis

For each health outcome (HO), incidence rates were calculated for the risk (i.e. 1–42 days) and the postvaccination comparison (i.e. 91–180 days) periods as the number of first occurrences of the HO divided by the total person-time accrued from the study subjects under observation. The relative risk (RR), its 95% confidence interval (CI), and unadjusted two-sided p-value, estimated using the exact conditional method with mid-probability adjustment, were calculated. Separate analyses were conducted for hospitalizations

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