New Drug Review

Review of the Persistence of Herpes Zoster Vaccine Efficacy in Clinical Trials

Stephen J. Cook, PharmD[1]; and Dennis K. Flaherty, MS, PhD[2]

[1]*Pharmacy Practice Department, University of Charleston School of Pharmacy, Charleston, West Virginia; and* [2]*Department of Pharmaceutical and Administrative Sciences, University of Charleston School of Pharmacy, Charleston, West Virginia*

ABSTRACT

Purpose: The live attenuated herpes zoster vaccine* was approved for the prevention of shingles in 2006. Initial Phase III clinical trials proved vaccine efficacy persisted during the study duration; however, assessment of long-term efficacy required additional studies. This article reviews efficacy data for the zoster vaccine that have been published since 2004. It focuses on studies assessing declining vaccine efficacy.

Methods: MEDLINE, EMBASE, CENTRAL, and CINAHL databases were searched for zoster vaccine efficacy trials. Randomized controlled trials published from 2004 to 2015 were included in the review.

Findings: Six studies were included in the review. The zoster vaccine reduced the risk of herpes zoster by 51.3% to 72.4% in 2 Phase III trials. Primary and other analyses showed the vaccine was effective at reducing the burden of illness (61.1%), postherpetic neuralgia (66.5%), disease interference on functional status (66.2%), and disease impact on health-related quality of life (55%) compared with placebo. Surveillance studies showed a decrease in vaccine efficacy for reducing the incidence of herpes zoster during follow-up years 3.3 to 7.8 (39.6% relative reduction) and 4.7 to 11.6 (21.1% relative reduction).

Implications: Initial zoster vaccine efficacy is significant, but declines in post-vaccination years 3 to 11. This raises the question about the need for possible revaccination with the zoster vaccine. Clinicians should consider the declining efficacy when administering the zoster vaccine to patients. Future studies will need to address the impact of the varicella vaccine on the incidence of shingles and whether this impacts the efficacy of the zoster vaccine. (*Clin Ther*. 2015;37:2388–2397)

Key words: vaccine, herpes zoster, shingles.

INTRODUCTION

The varicella zoster virus or human herpes virus 3 causes classical varicella (chicken pox) on initial exposure. Like other members of the herpes virus family, varicella zoster virus can infect and become dormant in the dorsal trunk; the third, fourth, sixth, or seventh cranial nerves; and the enteric (gastrointestinal) ganglia.[1] Reactivation as herpes zoster (HZ) virus occurs when cell-mediated immunity in older individuals declines to an unknown critical level.[2] There is also a significantly higher risk of HZ reactivation in immunosuppressed transplant recipients and individuals with HIV or cancer.[3]

HZ reactivation manifests in several different clinical syndromes. Vesicular eruptions occur along sensory nerve paths in the dorsal trunk, resulting in HZ (shingles) and postherpetic neuralgia (PHN). This painful condition, which is common in patients older than 80 years of age, can persist for months or years.[4] Eruptions in the third, fourth, sixth, or seventh cranial nerves are associated with ophthalmic involvement or peripheral facial weakness (Ramsay Hunt syndrome).[1,5,6,7] HZ in enteric ganglia can also be associated with intestinal diseases, such as achalasia, gastric ulcers, and colonic pseudo-obstruction (Ogilvie

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syndrome).[6,7,8] In immunosuppressed individuals, HZ often disseminates to the brain, where it causes a multifocal vasculopathy that mimics giant cell arteritis of cerebral arteries.[9,10]

It is difficult to determine the number of HZ cases that occur each year. Data from administrative code studies produce widely divergent estimates that depend on the method that health care providers choose to document and identify complications.[11] Some studies indicate HZ affects approximately 600,000 to 1,000,000 people in the United States each year.[12,13] More than 50% of these people are older than 60 years of age.[13] The lifetime risk of developing HZ has been estimated at 25%.[9] Individuals reaching 80 years of age have a 25% to 50% lifetime risk of developing HZ.[10]

The zoster vaccine live* was licensed in 2006 for prevention of shingles and postherpetic neuralgia in immunocompetent persons older than 60 years of age. It contains an attenuated vOka varicella strain that is also used in the varicella virus vaccine live† (chickenpox) vaccine.[14] Virus concentration is the major difference between the 2 vaccines. The zoster vaccine live contains 14-fold more virus when compared with the varicella virus vaccine live.[15,16] Both reconstituted vaccines also contain small amounts of sucrose, processed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium diphosphate, potassium phosphate, potassium chloride, trace quantities of residual components of MRC-5 cells (DNA and protein), EDTA, neomycin, and fetal bovine serum.[3]

In normal, healthy individuals, the HZ vaccine has few serious side effects. Injection site effects, including erythema, swelling, pain, and tenderness, were reported in 48% of those vaccinated. These effects were more common in persons aged 60 to 69 years old than in persons older than 70 years of age. Only 1.4% of vaccinated recipients reported serious side effects.[17]

The persistence of vaccine efficacy has been questioned in recent years. Since the initial Phase III trial, 2 vaccine persistence studies have been published.[18,19] The purpose of this article is to review the efficacy of zoster vaccine, including its long-term effectiveness.

METHODS

MEDLINE, EMBASE, CENTRAL, and CINAHL databases were searched for the terms *zoster vaccine*, *shingles vaccine*, and *Zostavax®*. Randomized controlled trials from January 1, 2004 to March 31, 2015 that evaluated efficacy were included in the review. Studies with populations older than 49 years of age were included. Efficacy trials that did not include clinical outcomes were excluded from consideration.

RESULTS

The final review included 6 studies; 3 of those studies were supplemental studies to an original Phase III trial.[14,18-22] Two studies were analysis of surveillance data to determine the persistence of vaccine efficacy. Excluded trials included 13 studies evaluating the immune response or immunogenicity for the zoster vaccine that were not tied to clinical end points and 4 trials strictly evaluating safety profile.

Efficacy

Efficacy can be measured by a number of different methods. Most pediatric and adult vaccines use prevention of disease as an efficacy index.[16,23] The shingles vaccine uses both prevention of disease and burden of illness (BOI) as efficacy end points. BOI is determined by averaging pain severity and duration scores based on the Zoster Brief Pain Inventory (ZBPI). The ZBPI is a patient-reported pain-rating tool for HZ rashes that uses a Likert scale for pain severity and pain-related interferences on functional activities. Which of the measurements, BOI or disease prevention, is the most relevant end point depends on the reader's perspective.[14,20] Table I summarizes the reviewed studies and their primary end points.

Burden of Illness

Shingles Prevention Study

Efficacy as estimated by the BOI was determined in 3 different studies: the Shingles Prevention Study (SPS), Short-Term Persistence Sub-Study (STPS), and the Long-Term Persistence Study (LTPS). The SPS was the first large randomized clinical trial to prove the efficacy of the zoster vaccine.[14] This multicenter, randomized, double-blinded, placebo-controlled trial enrolled 38,546 patients 60 years of age and older with a history of varicella. Participants were randomized 1:1 to receive a single subcutaneous 0.5-mL injection of the live attenuated Oka/Merck varicella zoster vaccine, with each dose containing 18,700 to 60,000 plaque-forming units, or placebo. Each group was stratified into 2 age categories, 60 to 69 years and $\geq$70 years of age. Patient demographic characteristics were similar between the study

*Trademark: Zostavax® (Merck, Kenilworth, New Jersey).
†Trademark: Varivax® (Merck, Kenilworth, New Jersey).