

Safety of Zoster Vaccine in Elderly Adults Following Documented Herpes Zoster

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Background. After completion of the Shingles Prevention Study (SPS; Department of Veterans Affairs Cooperative Studies Program Number 403), SPS participants who had

initially received placebo were offered investigational zoster vaccine without charge. This provided an opportunity to determine the relative safety of zoster vaccine in older adults following documented herpes zoster (HZ).

Methods. A total of 13 681 SPS placebo recipients who elected to receive zoster vaccine were followed for serious adverse events (SAE) for 28 days after vaccination. In contrast to the SPS, a prior episode of HZ was not a contraindication to receiving zoster vaccine. The SPS placebo recipients who received zoster vaccine included 420 who had developed documented HZ during the SPS.

Results. The mean interval between the onset of HZ and the receipt of zoster vaccine in the 420 recipients with prior HZ was 3.61 years (median interval, 3.77 years [range, 3–85 months]); the interval was <5 years for approximately 80% of recipients. The proportion of vaccinated SPS placebo recipients with prior HZ who developed ≥ 1 SAE (0.95%) was not significantly different from that of vaccinated SPS placebo recipients with no prior history of HZ (0.66%), and the distribution of SAEs in the 2 groups was comparable.

Conclusions. These results demonstrate that the general safety of zoster vaccine in older persons is not altered by a recent history of documented HZ, supporting the safety aspect of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommendation to administer zoster vaccine to all persons ≥ 60 years of age with no contraindications, regardless of a prior history of HZ.

Keywords. zoster vaccine; herpes zoster; zoster vaccine safety; zoster vaccine in elderly persons; ACIP recommendations.

A large randomized double-blind placebo-controlled clinical trial, Department of Veterans Affairs Cooperative Study Program (VA CSP) Number 403: the Shingles Prevention Study (SPS), conducted in 38 546 ambulatory immunocompetent adults ≥ 60 years of age, demonstrated that a live attenuated Oka/Merck varicella zoster virus (VZV) vaccine (hereafter, “zoster vaccine”) reduced the burden of illness due to herpes zoster (HZ)-related pain and/or discomfort by 61%, the incidence of postherpetic neuralgia by 67%, and the incidence of HZ by 51% [1]. Vaccine efficacy is thought to result from a vaccine-induced increase in VZV-specific cell-mediated immunity [2–4]. Zoster vaccine (Zostavax, Merck Sharp & Dohme) was licensed by the US Food and Drug Administration in 2006 for the prevention of HZ in immunocompetent adults ≥ 60 years of age, and is recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices for routine administration to eligible adults ≥ 60 years of age,

Received 3 December 2012; accepted 6 February 2013; electronically published 30 April 2013.

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The Journal of Infectious Diseases 2013;208:559–63

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2013.

DOI: 10.1093/infdis/jit182

regardless of a prior history of HZ [5, 6]. The rationale for administration of zoster vaccine irrespective of prior HZ includes the (1) questionable reliability of a self-reported history of HZ, (2) assumption that prior HZ will not increase the incidence or severity of adverse events associated with administration of zoster vaccine, and (3) lack of knowledge regarding the level and duration of protection induced by an episode of HZ. Data from the SPS indicate that increased levels of VZV-specific cell-mediated immunity induced by zoster vaccine or HZ often decline significantly to near baseline levels within 3 years after vaccination or HZ [3, 4]. Because subjects with prior HZ were excluded from the SPS, there is little direct evidence of the safety of zoster vaccine in subjects with prior HZ. A small study comparing zoster vaccine to placebo in 101 adults ≥ 50 years of age, all with a history of HZ ≥ 5 years prior to vaccination, indicated that the vaccine was well tolerated and boosted titers of VZV antibody [7]. Beginning in 2005, SPS participants who had received placebo and could be contacted were offered zoster vaccine without charge, in accordance with the SPS protocol [1]. Because 420 of the 13 681 placebo recipients who received zoster vaccine had experienced an episode of documented HZ during the SPS, we compared the safety of zoster vaccine in these 420 subjects with documented HZ to the safety of zoster vaccine in the 13 261 SPS placebo recipients who had never experienced HZ.

METHODS

Study Population

A substudy (clinical trials registration NCT00007501) was initiated in 2005 to provide zoster vaccine to SPS subjects who received placebo in the pivotal efficacy trial [1]. Investigational zoster vaccine was used because, although this vaccine had demonstrated efficacy in the SPS, it had not yet been approved by the Food and Drug Administration and was not commercially available when the substudy began. SPS placebo recipients who met entry criteria were offered zoster vaccine without charge and were vaccinated after providing signed informed consent in accordance with a protocol approved by the VA CSP Coordinating Center (CSPCC) Human Rights Committee and institutional review boards at each of the 22 SPS sites. Exclusion criteria were the same as those in the SPS, except that vaccine could be administered to nonambulatory subjects who presented to a SPS clinic and to placebo recipients who had developed documented HZ during the SPS. The study population consisted of 13 681 (80.5%) of the 17 002 SPS placebo recipients who could be contacted to receive zoster vaccine between October 2005 and May 2007, including 420 who had developed documented HZ during the SPS. The 13 261 placebo recipients without prior HZ served as a comparator group for the 420 with prior documented HZ. The 420 HZ cases were confirmed by SPS protocol procedures: 393 (94%) by identification of wild

type VZV DNA in specimens from rash lesions, 4 (1%) by the isolation of VZV from rash lesions, and 23 (5.5%), for whom rash lesion specimens were absent or inadequate, by clinical evaluation committee adjudication [1, 8].

Vaccine

The investigational zoster vaccine contained a minimum of 19 400 plaque-forming units of live attenuated Oka/Merck VZV per dose at expiry, comparable to the investigational zoster vaccine used in the SPS and to the commercial formulation subsequently licensed by the Food and Drug Administration [5]. Procedures for vaccine storage, reconstitution, and administration were identical to those used in the SPS [1].

Safety Surveillance

Subjects were instructed to immediately notify study personnel of all serious adverse events (SAEs) that occurred from the day of vaccination (day 0) through day 28 after vaccination. The study site physician-investigators, who were not blinded to the prior occurrence of HZ, evaluated each SAE for severity, seriousness, duration, and probability of being vaccine-related. Adverse Event Report and MedWatch Forms were completed for every SAE reported through day 28 after vaccination and reviewed by the VA CSP Central Research Pharmacy, the VA CSPCC, the study chairman, and Merck Sharp & Dohme (the holder of the investigational new drug application). Except for the shorter period of safety assessment (28 vs 42 days), these procedures were identical to those used in the SPS. After this review, MedDRA and COSTART codes were assigned to each SAE. No data were collected on nonserious injection-site or systemic adverse events. All vaccinated subjects were contacted by telephone on day 29 after vaccination to inquire about any SAE not previously reported, and any such SAEs were evaluated and reported as described above. Although there was no active SAE surveillance beyond day 28 after vaccination, any subsequent SAE that was passively ascertained and judged by the investigator to be possibly, probably, or definitely related to vaccination was reported as described above.

Statistical Methods

The proportions of subjects experiencing an SAE were compared between subjects with and those without prior HZ, using the Fisher exact test for the difference in proportions. A comparison was done within age stratum at time of SPS randomization and within age groups at time of vaccination. Mean age at vaccination was compared between groups using the Student's *t* test.

RESULTS

Demographic Characteristics

All 420 SPS placebo recipients with a history of documented HZ and 13 254 (99.9%) of the 13 261 SPS placebo recipients

Table 1. Safety Outcomes of Shingles Prevention Study (SPS) Placebo Recipients Receiving Investigational Zoster Vaccine Upon Completion of the SPS, by History of Documented Herpes Zoster (HZ) During the SPS and Short-Term Persistence Substudy

Variable	Subjects With No Prior History of HZ	Subjects With Prior History of HZ	<i>P</i> ^a
SAEs			
Overall	111/13 254 (0.84)	4/420 (0.95)	
≥1 ^b	88/13 254 (0.66)	4/420 (0.95)	.37
By COSTART body system^c			
General body	24/13 254 (0.18)	1/420 (0.24)	.54
Cardiovascular	27/13 254 (0.20)	1/420 (0.24)	.58
Digestive	11/13 254 (0.08)	0/420	>.99
Hematologic/lymphatic	2/13 254 (0.02)	0/420	>.99
Genitourinary	12/13 254 (0.09)	0/420	>.99
Metabolic/nutritional	5/13 254 (0.04)	0/420	>.99
Musculoskeletal	5/13 254 (0.04)	0/420	>.99
Nervous	10/13 254 (0.08)	1/420 (0.24)	.29
Respiratory	10/13 254 (0.08)	0/420	>.99
Skin	3/13 254 (0.02)	0/420	>.99
Site/sense	2/13 254 (0.02)	1/420 (0.24)	.089
By age in years			
At SPS enrollment^d			
60–69	45/7927 (0.57)	2/254 (0.79)	.66
≥70	43/5327 (0.81)	2/166 (1.20)	.40
At vaccination			
64–75	46/8098 (0.57)	2/250 (0.80)	.66
≥76	42/5156 (0.81)	2/170 (1.18)	.65
Years of age at zoster vaccination, mean ± SD	74.2 ± 5.9	74.2 ± 5.7	.89 ^e

Data are number of subjects with the characteristic/number at risk (%), unless otherwise indicated. A total of 18 521 SPS placebo recipients had no prior history of HZ, and 755 had a prior history; of these, 16 331 and 671, respectively, were contacted for zoster vaccination. A total of 13 261 SPS placebo recipients with no prior history of HZ received zoster vaccine, and 420 with a prior history of documented HZ received zoster vaccine; of these 13 254 (99.9%) and 420 (100%), respectively, completed follow-up for safety outcomes.

Abbreviation: SAE, severe adverse event.

^a By the Fisher exact test, unless otherwise indicated.

^b Compared with SPS vaccine recipients (table 3 in [9]), of whom 1.37% had ≥1 SAE during the first 43 days after vaccination (0.92% weighted for the first 29 days).

^c The data are comparable between vaccinated SPS placebo recipients with and those without prior HZ. They are also similar to those of the original SPS zoster vaccine recipients (table 3 in [9]), of whom 0.23% had a general body SAE during the first 43 days after vaccination (0.16% weighted for 29 days), and 0.43% had a cardiovascular SAE during the first 43 days after vaccination (0.35% weighted for 29 days).

^d Values were 1.12% during the first 43 days after vaccination (0.75% weighted for 29 days) for SPS vaccine recipients aged 60–69 years and 1.66% during the first 43 days after vaccination (1.11% weighted for 29 days) for SPS vaccine recipients aged ≥70 years.

^e By the Student *t* test.

without a history of HZ completed post-vaccination. Years of age safety follow-up. There was no difference in the mean age

Table 2. Time From Onset of Herpes Zoster (HZ) to Zoster Vaccination Among 420 Placebo Recipients With a History of Documented HZ During the Shingles Prevention Study

Time	Subjects With Prior History of HZ
Overall, years	
Mean ± SD	3.61 ± 1.62
Median (range)	3.77 (3–85 months)
0–1 y	62 (14.8)
>1–2	13 (3.1)
>2–3	40 (9.5)
>3–4	126 (30.0)
>4–5	94 (22.4)
>5–6	69 (16.4)
>6–7	14 (3.3)
>7	2 (0.5)

The times from onset of HZ to zoster vaccination for the 4 subjects with a severe adverse event after receipt of zoster vaccine were 63, 49, 42, and 11 months.

(±SD) at the time of vaccination between vaccinated placebo recipients with and those without prior HZ (74.2 ± 5.7 and 74.2 ± 5.9 years, respectively; *P* = .89; Table 1). The average age in each group at the time of zoster vaccination was approximately 4.8 years older than the average age at vaccination of SPS zoster vaccine recipients (69.4 ± 6.3 years). The proportion of placebo recipients who were ≥76 years of age when they received zoster vaccine was also similar among the 420 subjects with a history of documented HZ and the 13 261 subjects without a history of HZ (40% and 39%, respectively). The mean interval between the onset of their HZ rash and the administration of zoster vaccine among the 420 subjects with prior HZ was 3.61 years (median interval, 3.77 years [range, 3–85 months]); the interval was <5 years for approximately 80% of the 420 recipients (Table 2).

SAEs

During the 28 days following vaccination, a total of 4 SAEs were reported among 4 of the 420 subjects with prior HZ, compared with 111 SAEs among 88 of the 13 261 subjects with no history of HZ. The proportion of vaccinated placebo recipients with ≥1 SAE was not significantly different among those with or without prior HZ (0.95% and 0.66%, respectively; *P* = .37) and was comparable to that in SPS vaccine recipients during the first 28 days after vaccination (0.91%; Table 1). The most frequently reported SAEs, by COSTART body system, were general body and cardiovascular. The proportion of subjects with general body SAEs was comparable in the 2 groups (0.24% and 0.18% among subjects with and those without prior HZ, respectively; *P* = .54). The proportion of subjects with cardiovascular SAEs was also comparable in the 2 groups (0.24% and

0.20% among subjects with and those without prior HZ, respectively; $P = .58$). These results are comparable to those observed for SPS vaccine recipients (Table 1). None of the SAEs among the 420 vaccine recipients with prior HZ (an ocular blood clot, an acute subarachnoid hemorrhage, an episode of extreme fatigue, and a myocardial infarction resulting in hospitalization) were considered to be related to zoster vaccine. Among the 88 vaccine recipients with no prior HZ and ≥ 1 SAE, 9 SAEs in 4 subjects were considered possibly related to zoster vaccine (peripheral neuritis in 1 subject, fever in 1, and multiple symptoms in 2 [vertigo, nausea, and vomiting in one and vertigo, hearing loss, syncope, and vomiting in the other]).

The SAEs were also examined with regard to age at the time of the SPS enrollment (60–69 and ≥ 70 years of age), as well as age at the time of zoster vaccination (64–75 and ≥ 76 years of age). The incidence of SAEs was comparable in both age cohorts (Table 1).

There was no systematic attempt to collect data on nonserious adverse systemic events or injection-site complications. However, there were no unsolicited reports of serious or unexpected injection-site complaints in either group following administration of zoster vaccine, and none were reported during telephone interviews on day 29 after vaccination.

DISCUSSION

Administration of zoster vaccine to SPS placebo recipients provided an opportunity to assess the safety of zoster vaccine administration to older individuals following a documented episode of HZ, of which $>80\%$ of episodes occurred <5 years before vaccination (Table 2). These results complement the study by Mills et al, who assessed safety in vaccine recipients, all of whom had HZ >5 years prior to vaccination [7]. Detailed examination of zoster vaccine safety during the 42 days after vaccination in the SPS revealed that SAEs occurred in 1.37% of subjects (0.91% in the first 28 days) and that mild injection site reactions were seen in about half of vaccine recipients [9]. Furthermore, during the SPS, all 918 HZ cases that were positive for VZV DNA by polymerase chain reaction analysis contained wild-type VZV DNA; none contained Oka vaccine strain VZV DNA [8].

This study provides the only direct evidence supporting the safety of zoster vaccine administered irrespective of a prior history of HZ, as it compares subjects with and those without a prior episode of documented HZ who received zoster vaccine. We demonstrated that zoster vaccine was generally safe and well tolerated, both in the 420 SPS placebo recipients with documented HZ during the SPS and in the 13 261 comparable SPS placebo recipients with no prior history of HZ. The proportion of placebo recipients with proven HZ prior to zoster vaccination who reported ≥ 1 SAE during the 28 days after vaccination (0.95%) was similar to that for vaccinated SPS placebo

recipients without prior HZ (0.66%) and during the 28 days after vaccination among SPS subjects who received zoster vaccine at enrollment (0.91%; Table 1), despite the fact that the SPS placebo recipients in the current study were ≥ 5 years older when they received zoster vaccine. Furthermore, the nature and distribution of SAEs were similar in vaccinated SPS placebo recipients with and those without prior HZ, as well as in the original SPS vaccine recipients (Table 1).

An important limitation of our study is that it was an open-label study. Thus, subjects and study personnel were aware of who did and who did not have prior HZ. In addition, only SAEs were recorded, and vaccinees were followed for only 28 days after vaccination. In the SPS, subjects were followed for 42 days after vaccination for SAEs and also for nonserious safety outcomes. However, the excellent safety profile of zoster vaccine demonstrated in previous studies did not give reason to extend the safety assessment period beyond 28 days. This study did not evaluate vaccine efficacy or the potential benefit of administering zoster vaccine to subjects with a recent history of HZ.

In conclusion, the safety of zoster vaccine when administered to older adults with a recent history of documented HZ appears to be equivalent to that when zoster vaccine is administered to comparable adults with no prior history of HZ. These results support the safety aspect of the Advisory Committee on Immunization Practices recommendation to administer zoster vaccine to all persons ≥ 60 years of age who have no contraindications, including those with a previous episode of HZ [6].

Notes

Acknowledgments. The study was conducted by the Cooperative Studies Program, Department of Veterans Affairs, Office of Research and Development. Additional support was provided by Merck Sharp & Dohme, by the James R. and Jesse V. Scott Fund for Shingles Research, and by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health. Data management and analysis support was provided at West Haven CSPCC by Karen Dellert and Kathy Newvine.

The Shingles Prevention Study was planned and/or administered by a planning/executive committee, the members of which are as follows: Michael N. Oxman (chair), Robert Arbeit, Patricia Barry, Chris Beisel, Kathy D. Boardman, Cindy L. Colling, Larry Davis, Lawrence Gelb, Anne A. Gershon, Anthony R. Hayward, Michael R. Irwin, Gary R. Johnson, Myron J. Levin, Peter N. Peduzzi, Kenneth Schmader, Michael S. Simberkoff, Stephen E. Straus, Adriana Weinberg, Heather M. Williams, Jeffrey L. Silber, Paula W. Annunziato, Christina Y. Chan, and Ivan S. F. Chan.

The Vaccination of Placebo Recipients Substudy was planned and/or administered by the Shingles Prevention Study Executive Committee and representatives from Merck Sharp & Dohme.

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Potential conflict of interest. M. J. L. claims intellectual property in a Merck Sharp & Dohme patent on the use of zoster vaccine to prevent HZ. M. J. L. and K. E. S. receive research funds and/or consultation fees from or serve on the speakers bureau of Merck Sharp & Dohme. I. S. F. C., J. L. S., and P. W. A. are employees of Merck Sharp & Dohme and may hold stock and/or stock options in the company. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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