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Optimal Timing of Zoster Vaccination After Shingles: A Prospective Study of the Immunogenicity and Safety of Live Zoster Vaccine

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ABSTRACT

Background: Zoster vaccination is recommended for people with a history of herpes zoster (HZ), but the most effective timing of vaccine administration after zoster illness is unresolved. This prospective observational study compared the immunogenicity and safety of administering HZ vaccine at 6-12 months and 1-5 years after zoster illness.

Materials and Methods: Blood samples were collected before the administration of live zoster vaccine and 6 weeks after vaccination. Varicella-zoster virus (VZV) IgG concentrations and T-cell responses were assessed by glycoprotein enzyme-linked immunosorbent assay and interferon-γ enzyme-linked immunospot assay (ELISPOT), respectively.

Results: The baseline geometric mean value (GMV) of VZV IgG was higher in the 6-12 months group than in the 1-5 years group (245.5 IU/mL *vs.* 125.9 IU/mL; *P* = 0.021). However, the GMV increased significantly in both groups (*P* = 0.002 in the 6-12 months group; *P* <0.001 in the 1-5 years group). The results of the ELISPOT assay were not significant for differences of the GMV between baseline and 6-week post-vaccination groups, while the GMV increased significantly in both groups (*P* = 0.001 in the 6-12 months group; *P* <0.001 in the 1-5 years group).
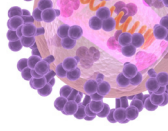
Conclusion: The immunogenicity of zoster vaccine may be similar whether administered 6-12 months, or >1 year after zoster illness.

Trial Registration: ClinicalTrials.gov Identifier: NCT02704572

Keywords: Zoster vaccine; Herpes zoster; Immunogenicity; Enzyme-linked immunosorbent assay; Enzyme-linked immunospot assay

INTRODUCTION

Herpes zoster (HZ) is a common disease that affects 25 to 35% of the population [1, 2]. Typically, clinical manifestation presents as a vesicular rash, generally limited to a single dermatome and accompanied by aching pain or burning sensation. The most common HZ complication is postherpetic neuralgia, which is a chronic neuropathic pain persisting >120 days after the onset of rash [3]. Major risk factors are increasing age and unvaccinated persons aged >85 years old who have an approximately 50% risk of developing HZ disease [4]. Moreover, recurrent HZ occurs in approximately 6.2% of persons with a history of the

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disease [5]. Zoster vaccine reduces the development of HZ and postherpetic neuralgia and is recommended for all immunocompetent adults aged ≥60 years [6]. Zoster vaccine has an immune boosting effect in persons with a history of HZ disease [7] and reduces the rate of recurrence in immunocompetent individuals [8]. As a result, current guidelines recommend the vaccination of persons with a history of zoster [6, 9-12].

However, the timing of zoster vaccination following a HZ episode is unclear. The United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practices does not specify vaccine administration timing for those with a history of zoster [6], while both the Australian Immunization Handbook and Canada's National Advisory Committee on Immunization suggest vaccinating at least 1-year after a HZ episode [9, 10]. Public Health England also recommends that immunocompetent individuals who develop zoster illness should delay zoster vaccination for 1 year [11]. However, these recommendations assume that vaccine efficacy could be reduced because of varicella-zoster virus (VZV) boosted immunity. Therefore, it is necessary to scientifically determine the most effective time for zoster vaccination.

The objective of this study was to compare immune response and safety based on the timing of vaccine administration after HZ illness. Therefore, we conducted a prospective study to assess cellular and humoral immune responses and collected adverse event information related to immunocompetent subjects.

MATERIALS AND METHODS

1. Subjects and vaccination

This study assessed both the immune response to HZ vaccination at 6 weeks and vaccination safety in relation to administration timing following HZ illness. The study was conducted from January 2016 to December 2016. The study enrolled adults who provided written informed consent and who were aged ≥50 years with a physician confirmed diagnosis of HZ illness within the previous 0.5-5 years. Potential subjects who met any of the following criteria were excluded: 1) known contraindication to live zoster vaccination, 2) previous recipient of zoster vaccine, 3) history of taking immunosuppressive drugs such as cytotoxic chemotherapy or corticosteroids, 4) a CD4 cell count <500/mm³ in the setting of HIV infection, 5) organ transplantation, 6) autoimmune disease, or 7) other conditions that cause an abnormal immune response to vaccination such as fever on the day of vaccination or having received other vaccinations within the prior month.

To analyze immune response and vaccine administration safety, study subjects were divided into one of two groups based on whether they received vaccine at 6-12 months or 1-5 years after zoster illness. Subjects who had a HZ episode 12 months earlier were included in the 6-12 months group. In addition, subgroup analysis was performed that divided the period of 1-5 years into 1-3 years (13-36 months) and 3-5 years (>36 months).

Zostavax® (Merck Sharp & Dohme Corp, Rahway, NJ, USA) is a live, attenuated VZV vaccine that was administered as a one-time subcutaneous injection of 0.65 mL containing 19,400 plaque-forming units of the Oka/Merck strain. Blood samples were collected before and 6 weeks after vaccination; peripheral blood mononuclear cells (PBMCs) and serum were immediately separated and stored in liquid nitrogen and –70°C, respectively.

This study was approved by the institutional review board of Seoul National University Hospital (IRB No. 1511-046-718) and registered at ClinicalTrials.gov (number: NCT02704572).

2. Immunologic assessments

Titers of IgG antibodies against VZV glycoprotein were measured using SERION ELISA classic VZV IgG (gpELISA) (Institute Virion\Serion, Würzburg, Germany) according to the manufacturer's instructions. Briefly, serum samples were diluted (1:1,000) and added in duplicate into a 96-well plate that was coated with VZV-specific antigens and then incubated at 37°C for 1 h. After washing, a solution of anti-human IgG antibody conjugated to alkaline phosphatase was added and incubated at 37°C for 30 min. Following this, it was incubated with a para-nitrophenyl phosphate solution at 37°C for 30 min. Optical density was measured at 405 nm using a VersaMax microplate spectrophotometer (Molecular Devices Corporation, San Jose, CA, USA) and antibody titer was quantified using a lot-specific standard curve based on a 4-parameter logistic function.

The VZV-specific interferon gamma (IFN-γ) enzyme linked immunosorbent spot (ELISPOT) assay was performed using an IFN-γ ELISPOT set (BD Bioscience, San Jose, CA, USA) as previously described [12]. Briefly, the 96-well plates were coated with anti-human IFN-γ monoclonal antibody (BD Bioscience) and then incubated overnight. The wells were blocked for 2 h with culture medium containing 10% fetal bovine serum and complete medium containing an ultraviolet-inactivated preparation of VZV antigen (VR-916, American Type Culture Collection, Manassas, VA, USA).

A 100-μL suspension of PBMCs of 10^7 PBMCs/mL was added to each well, and plates were incubated for 16 to 20 h at 37°C and 5% CO_2 in 95% humidity. Next, 100 μL of biotinylated anti-human IFN-γ antibody were added to each well. Plates were incubated for 2 h at 4°C, washed, and developed with streptavidin-horseradish peroxidase and substrate (AEC Substrate Reagent Set, BD Bioscience). The resulting spots were enumerated by an automated microscope (CRL ImmunoSpot S4Core Analyzer, Cellular Technology ltd. Cleveland, OH, USA). The VZV-specific responses were reported as the number of spot-forming cells (SFCs) per 10^6 PBMCs based on an SFC count in response to VZV antigen minus the SFC count in response to MRC-5 cell antigen. Samples with a poor response to phytohemagglutinin (<300 SFCs/10^6 PBMCs) were excluded from the analysis.

3. Safety assessment

We evaluated vaccine safety with a self-reported structured questionnaire and medical interview 6 weeks after vaccination to identify the type and severity of any local and systemic adverse events. Adverse events were graded using United States Food and Drug Administration standard toxicity scale [13]. The relationship between adverse events and vaccination was divided into three categories: unlikely, possible, or likely. A vaccine-related adverse event was defined as having a possible or likely relationship.

4. Statistical analysis

The VZV-specific IgG levels and SFCs of the ELISPOT assay were presented as the geographic mean value (GMV) and geometric mean ratio of values at baseline and 6 weeks after vaccination (the geographic mean fold rise [GMFR]). GMV and GMFR were compared using the Wilcoxon signed-rank test. The Mann-Whitney *U* test was used to compare other continuous variables and the Chi-square test or Fisher's exact test was used for categorical variables, when appropriate. All tests were two-sided, and *P* <0.05 was considered

significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Subjects

A total of 60 subjects were enrolled in the study (**Supplementary Fig. 1**). One person in the 1-5 years group was excluded due to loss to follow-up and the data for 59 subjects were used in the final analysis. The median age was 63 years (range, 50-84) with 42 subjects (71.2%) <70 years old and 17 (28.8%) ≥70 years old (**Table 1**). Thirty-nine subjects (66.1%) were female. Participants in each group were not significantly different with respect to age, sex, and underlying disease other than hypertension ($P = 0.018$) and diabetes mellitus ($P = 0.025$) which were more frequent in the 6-12 months group (**Table 1**, **Supplementary Table 1**). Following zoster illness, 18 and 41 subjects were vaccinated from the 6-12 months and 1-5 years groups, respectively. A 66-year-old male subject with hypertension in the 6-12 months group had disseminated HZ from the buttocks to trunk and neck. Before the study, one subject from each group had a history of two HZ episodes. One subject, from the 6-12 month group, was a 71-year-old female with hypertension whose HZ first developed 10 years ago then relapsed on her left chest 11 months before study enrollment. The subject in the 1-5 years group was a 61-year-old female without underlying medical condition, whose HZ first developed 30 years ago then relapsed on her left flank 4 years before the study.

2. Immunologic assessments

The baseline GMV of VZV-specific IgG was 154.88 IU/mL (95% confidence interval [CI], 123.03-194.98) and was significantly higher in the 6-12 months group than the 1-5 years group (245.47 IU/mL *vs.* 125.89 IU/mL, $P = 0.021$) (**Table 2**). Six weeks after vaccination, the GMVs increased significantly in both groups ($P = 0.002$ in the 6-12 months group, $P < 0.001$ in the 1-5 years group). The GMVs at 6 weeks were not significantly different between groups (346.74 IU/mL *vs.* 309.03 IU/mL, $P = 0.569$). Meanwhile, the GMFR was significantly lower in the 6-12 months group than in the 1-5 years group (1.41 *vs.* 2.45, $P = 0.002$). The percent of subjects with a GMFR >4 was lower in the 6-12 months group than in the 1-5 years group but was not statistically significant (5.6% *vs.* 24.4%, $P = 0.146$).

The IFN-γ ELISPOT assay baseline GMV was 8.71 SFCs per 10^6 PBMCs (95% CI, 6.17-12.59) for the total study population. Six weeks after vaccination, the GMV significantly increased

Table 1. Clinical characteristics of subjects at baseline

Variable	All subjects	6–12 months after zoster (n = 18)	1–5 years after zoster (n = 41)	P-value
Age				
Median years (range)	63 (50–84)	68 (50–84)	62 (50–79)	0.564
Female sex	39 (66.1)	9 (50.0)	30 (73.2)	0.083
Median months after zoster (range)	25 (7–51)	9 (7–12)	40 (13–51)	<0.001
Disseminated zoster	1 (1.7)	1[a] (5.6)	0	0.305
Underlying disease				
Hypertension	9 (15.3)	6 (33.3)	3 (7.3)	0.018
Diabetes mellitus	3 (5.1)	3 (16.7)	0	0.025
Malignancy	1 (1.7)	0	1 (1.4)	>0.999
Hypothyroidism	1 (1.7)	1 (5.6)	0	0.305

[a]Herpes zoster rash started from the left buttock and progressed to the trunk and neck.
The value denotes the subject number (%) unless otherwise indicated.

Table 2. Varicella-zoster virus specific immune response

Variable	Vaccination timing after zoster illness				P-value
	6–12 months		1–5 years		
	No.	Value	No.	Value	
ELISA for IgG (IU/mL)					
Baseline GMV	18	245.47 (144.54–416.87)	41	125.89 (100.00–158.49)	0.021
Post-vaccination GMV	18	346.74 (229.09–537.03)	41	309.03 (251.19–371.54)	0.569
GMFR	18	1.41 (1.17–1.74)	41	2.45 (1.95–3.09)	0.002
GMFR >4	18	1 (5.6)	41	10 (24.4)	0.146
IFN-γ ELISPOT (SFC)					
Baseline GMV	16	7.76 (3.72–16.60)	35	9.12 (6.17–13.80)	0.673
Post-vaccination GMV	16	26.30 (15.14–45.71)	35	38.02 (28.84–51.29)	0.184
GMFR	16	3.39 (2.04–5.62)	35	4.17 (2.88–6.03)	0.507
GMFR >4	16	7 (43.8)	35	15 (42.9)	0.952

ELISA, enzyme-linked immunosorbent assay; GMV, geometric mean value; GMFR, geometric mean fold-rise; INF-γ ELISPOT, interferon-γ enzyme-linked immunosorbent spot; SFC, spot forming cell per 10^6 peripheral blood mononuclear cells.
Data represent the geometric mean (95% confidence interval) or No. (%).

to 33.88 SFCs per 10^6 PBMC cells (95% CI, 26.30-43.65, P <0.001). There was no significant difference in the GMV at baseline and 6 weeks after vaccination between groups and the GMVs increased significantly in both groups (P = 0.001 in the 6-12 months group, P <0.001 in the 1-5 years group) (**Table 2**). There were no significant differences between groups in the GMFR (3.39 *vs.* 4.17, P = 0.507), and the number of subjects with a GMFR >4 (43.8% *vs.* 42.9%, P = 0.952). Due to the lack of observed cells, eight samples could not be analyzed, resulting in the discrepancy of sample numbers when using ELISA and ELISPOT.

Subgroups were analyzed by dividing subjects into groups based on zoster vaccine administration time following zoster illness (6-12 months, 1-3 years, and >3 years), and this review showed that boosting effect in humoral and cellular immunity was comparable between the groups (**Fig. 1**).
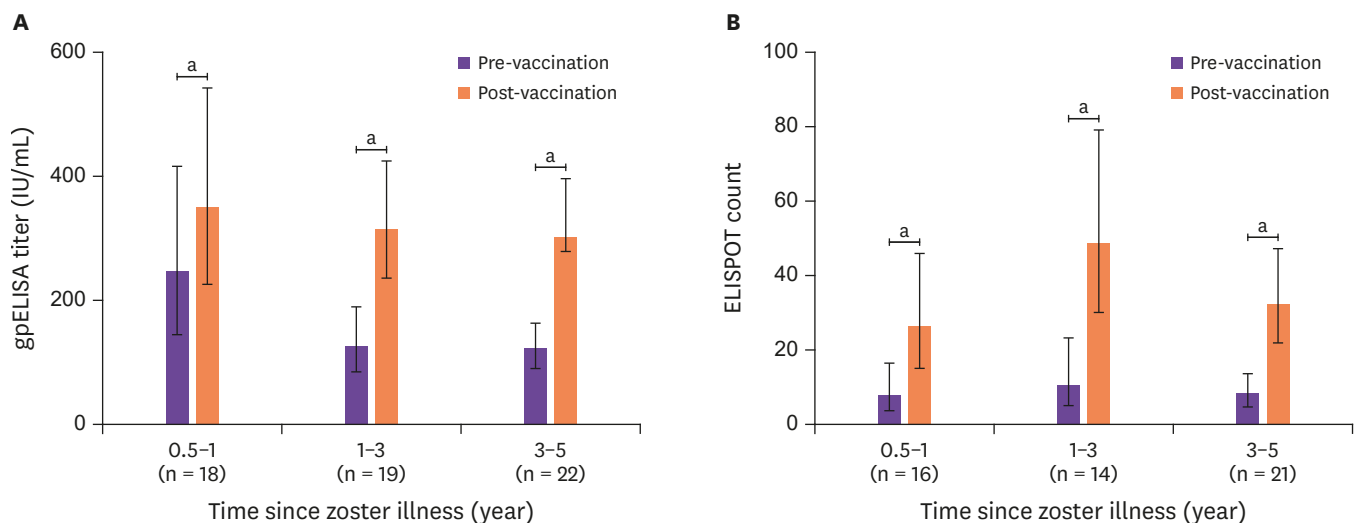

Figure 1. Varicella-zoster virus (VZV) specific immune responses according to zoster vaccine administration timing after zoster illness. The study population was divided into a before 1-year group (6-12 months), 1-3 years group (13-36 months), and >3 years group (>36 months). (A) Bars indicate geometric means and 95% confidence intervals (CI) for titers of enzyme-linked immunosorbent assay against VZV glycoproteins (gpELISA). (B) Bars indicate geometric means and 95% CIs for interferon-γ enzyme-linked immunospot (ELISPOT) counts, measured as spot-forming cells per 10^6 peripheral blood mononuclear cells.
[a]P <0.01.

3. Safety assessment

There were three cases of vaccine related adverse events during the study period: one person from each group had mild pain and tenderness at the injection site, and one subject from the 6-12 months group had mild nausea and vomiting. There were no cases of a zoster-like rash during the study period.

DISCUSSION

This prospective study showed that 6 weeks after the administration of live zoster vaccine to subjects with a 6-12 month or 1-5 year history of having had zoster illness experienced a significant increase of anti-VZV IgG levels measured by gpELISA and IFN-γ ELISPOT. In addition, the anti-VZV IgG levels and IFN-γ ELISPOT counts at 6 weeks were comparable between the groups, although baseline IgG levels were higher in the 6-12 months group than in the 1-5 years group.

Reactivation of VZV is known to be related to declining VZV-specific cell-mediated immunity [14, 15]. VZV-specific cellular immunity was reported to be induced similarly by zoster illness and zoster vaccination [16]. In the present study, cellular immunity was measured by the interferon-γ ELISPOT, which was significantly increased by zoster vaccination and was comparable 6 weeks after vaccination in both groups. These findings suggest that both groups had a similar likelihood of developing HZ after zoster vaccination.

Humoral immunity is less emphasized since the level of VZV-specific IgG is maintained with age [15], but some studies have reported the role of VZV-specific IgG in zoster illness. Gilbert et al. speculated that the increased fold change in gpELISA titers 6 weeks after vaccination correlates with zoster vaccine efficacy [17], and Levin et al. suggested that VZV-specific IgG correlates with cell-mediated immunity [18]. In the present study, the GMFR of IgG in gpELISA was higher in the >1-year group, although this result seems to be influenced by the higher baseline IgG titers in the 6-12 months group. However, as there was no significant difference in the absolute IgG titer after vaccination and the number of patients with a GMFR increase of >4 (43.8% in the 6-12 months group *vs.* 42.9% in the 1-5 years group), the difference in vaccine efficacy between the two groups seems not to be definite.

Analysis of both cellular and humoral responses to zoster vaccination reveals that vaccination administered ≥1 year after zoster illness may have similar immunogenicity responses. Our sub-analyses of groups vaccinated 1-3 years and 3-5 years after HZ also suggest that a vaccination delay of >3-years after zoster illness does not provide a cellular and humoral immune response advantage.

Previous prospective and retrospective observational studies suggest that patients who had a zoster illness within the previous year had a low rate of recurrence (0.4-0.8%) [19, 20]. These findings are compatible with our results showing that the anti-VZV IgG level was maintained until 1 year after zoster illness. Similarly, Tseng et al. reported that the recurrence rate of HZ was 0.1% during a 2-year follow-up of immunocompetent persons regardless of vaccination history [8]. However, the recurrence rates of HZ increased to 5.3% after a 20-year follow-up in long-term cohort studies [21]. Based on these epidemiological findings and data from the present study, the low recurrence rate in subjects with a recent HZ history might be associated with an immunologic boosting effect caused by the original zoster illness.

This study has several limitations. First, only the VZV-specific IFN-γ ELISPOT was used to evaluate VZV-associated cell-mediated immunity. Other methods, such as an intracellular cytokine assay, may show more details about the CD4/CD8 cell response and effector/memory cells. Second, confounding factors such as age, gender, and underlying disease might affect the results of this study because the number of subjects was small. However, a sub-analysis dividing study groups into those aged <70, and those ≥70 years of age, showed similar results (data not shown). Third, a reported diagnosis or history of HZ could be erroneous. However, one of the reasons for recommending zoster vaccination after HZ is that the previous illness may have been misdiagnosed. In addition, diagnosis of HZ is usually not made by laboratory tests in actual practice. Therefore, it may be reasonable to apply the results of this study to clinical practice. Fourth, long-term clinical data about HZ recurrence were not available. A large-scale study is needed to confirm the results of this study.

In conclusion, the immunogenicity of zoster vaccination administered 6-12 months after zoster illness may be similar to that administered >1 year after zoster illness.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Underlying diseases of subjects at baseline

Click here to view

Supplementary Figure 1
Flow chart of study design.

Click here to view

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