



Altered immunogenicity of 23-valent pneumococcal polysaccharide vaccine in elderly patients with diabetes who revealed lower responses to concomitant administration of BIKEN varicella zoster vaccine: Results of post hoc analysis of a randomized double-blind trial☆

Atsuko Hata ^{a,*}, Taisei Ishioka ^b, Kazunori Oishi ^c, Toshiro Katayama ^d, Takayoshi Ohkubo ^e

^a Department of Infectious Diseases, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka, Japan

^b Environmental Hygiene Division, Takasaki General Public Health Center, 5-28 Takamatsucho, Takasaki, Gunma 370-0829, Japan

^c Infectious Disease Surveillance Center, National Institute of Infectious Diseases, 1-23-1 Toyama Shinjuku-ku, Tokyo 162-8640, Japan

^d Department of Engineering, Faculty of Health Sciences, Morinomiya University of Medical Sciences, 1-26-16 Nankokita Suminoe-ku, Osaka 559-8611, Japan

^e Department of Hygiene and Public Health, Teikyo University School of Medicine, 2-11-1 Kaga Itabashi-ku, Tokyo 173-8605, Japan

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ABSTRACT

Aims: This double-blind randomized controlled study of 52 elderly patients with diabetes assessed cell-mediated immunity and safety of BIKEN varicella-zoster vaccine (BVZV). Cellular and humoral responses to VZV at 3 months after BVZV and 23-valent polysaccharide pneumococcal vaccine (PPSV23) vaccination elicited poor results. Post-hoc analyses assessed the effects of immunogenicity of PPSV23.

Methods: Using standardized enzyme-linked immunosorbent assay, pneumococcal 6B and 23F serotype-specific immunoglobulin G (IgG)-binding antibody concentrations were measured in stored samples retrospectively before administration and 3 months after. Responders increased more than twofold in at least one serotype-specific IgG.

Results: The geometric mean concentration ratio (GMCR) of serum anti-pneumococcal 6B IgG was 1.76 (95%CI: 0.58, 5.34) in patients receiving concurrent PPSV23 and BVZV, compared to 2.39 (95%CI: 0.53, 10.76) in patients receiving PPSV23 and placebo ($P = .055$). The GMCR of serum anti-pneumococcal 23F IgG was 2.54 (95%CI: 0.57, 11.43) in PPSV23/BVZV vaccinees compared to 3.34 (95%CI: 0.84, 12.92) in PPSV23/placebo vaccinees ($P = .424$). Responder rates, those who developed antibodies to either/both serotypes, were 68% in the BVZV group and 85% in the placebo group ($P = .007$).

Conclusions: Results suggest that concurrent administration of BVZV influenced humoral responses to PPSV23 in elderly subjects with diabetes.

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1. Introduction

Individuals with comorbid diseases including diabetes have an increased risk of acquiring herpes zoster (HZ) infection.^{1,2} An earlier study using interferon-gamma ELISPOT assay revealed that diabetics have significantly lower cell-mediated immunity (CMI) to VZV than healthy individuals.³ Another report described that the live Oka BIKEN varicella-zoster vaccine (BVZV) boosted virus-specific, cell-mediated,

and humoral immunity among elderly people with or without diabetes.⁴ We used interferon-gamma ELISPOT assay to demonstrate that BVZV enhances VZV-specific immunity in elderly people with or without diabetes.⁴

A double-blind randomized controlled study of 60–70-year-old patients with diabetes mellitus was conducted to evaluate the safety and cellular and humoral immunity to varicella zoster virus (VZV) after subcutaneous administration of one dose of live Oka BVZV or placebo concurrently with the 23-valent polysaccharide pneumococcal vaccine (PPSV23).⁵ The 54 participants who received either BVZV (27 participants) or placebo (27 participants) with the PPSV23 were evaluated using intent-to-treat analysis and per-protocol analysis. Antibody responses and VZV-specific CMI's were similar at baseline and after vaccination in both groups. However, the VZV-specific CMI's in all elderly and diabetic subjects was lower than expected based on other studies.^{3,4} We attributed the lower responses against BVZV in this population group to

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* Corresponding author at: Department of Infectious Diseases, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan.

E-mail address: ahata@kitano-hp.or.jp (A. Hata).

the following three points: (1) simultaneous administration of BVZV and PPSV23; (2) effects of using the DPP-4 inhibitor, which were not available when we performed the previous pilot study⁴, and (3) technical difficulties of measuring VZV-specific CMI using skin test and interferon-gamma ELISPOT assay. Both groups showed low responses to BVZV with simultaneous administration in the randomized controlled study.⁵ To further ascertain the effects of immunogenicity to PPSV23 with simultaneous vaccination of the BVZV, we applied post-hoc analysis to assess humoral immunity by measuring the concentrations of serotype-specific IgG in subjects with diabetes.

2. Participants and methods

2.1. Study population and design

Procedures of this study were described in an earlier report.⁵ Briefly, a double-blind randomized placebo-controlled study was conducted comprising of 62 eligible 60–70-year-old people with diabetes between March 2011 and January 2014 at Kitano Hospital. Participants who fulfilled the inclusion criteria were assigned randomly in a 1:1 ratio to receive BVZV and PPSV23 or placebo and PPSV23. The outcomes measured were changes in CMI on an in-vivo skin-test assay at 3 months after vaccination, humoral immunity to VZV at 3 months after vaccination, and safety. Of the 62 participants, 54 completed this study. The study was approved by the Tazuke Kofukai Medical Research Institute Ethics Committee (S15-07-003). This trial was registered in the UMIN Clinical Trials Registry System (UMIN00004771).

2.2. Vaccines administered

We used commercially available PPSV23 (Pneumovax® NP; Merck and Co. Inc., Tokyo, Japan) containing a mixture of 25 µg each of purified capsular polysaccharides from 23 serotypes of *Streptococcus pneumoniae*. This adjuvant-free PPSV23 was administered subcutaneously to all subjects to facilitate their participation. A live, attenuated Oka varicella vaccine® manufactured by the Research Foundation for Microbial Diseases of Osaka University (BIKEN) was used. To avoid confusion, we designated the Oka varicella vaccine® as a BIKEN varicella-zoster vaccine (BVZV). We administered the same dose of Oka varicella vaccine® given to children to prevent chickenpox in Japan. Sterile purified distilled water was used as a diluent for both the BVZV and placebo. We simultaneously administered PPSV23 with BVZV or placebo to elderly individuals because concurrent immunization is common practice and is recommended in Japan as a method to deliver vaccines. Simultaneous immunization (two or more simultaneous vaccinations of one subject, except when using a mixed vaccine) can be done when a doctor deems it necessary (<https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000036493.html>).

2.3. Study objectives

This post-hoc study was designed to evaluate the effects of anti-PPSV23 immune response in 25 participants who received concomitant administration of PPSV23 and BVZV (group 1), compared with 27 participants who received PPSV23 and placebo (group 2), as reported for an earlier study.⁴

2.4. Immunogenicity assessment

Using standardized enzyme-linked immunosorbent assay (ELISA), pneumococcal serotype-specific immunoglobulin G (IgG)-binding antibody concentrations before and 3 months after administration were measured retrospectively in samples stored at -80°C . The 6B and 23F serotype-specific IgG concentrations were ascertained according to the WHO ELISA protocol available at <http://www.vaccine.uab.edu/#>. Results were summarized for each serotype using geometric mean

concentrations (GMCs). Fold increases relative to pre-vaccination values (post-vaccination value to pre-vaccination value ratios) for each serotype were compared between groups using geometric mean concentration ratios (GMCRs). A positive antibody response was defined as a two-fold or greater increase in IgG concentration.^{6,7}

2.5. Evaluation of responders

We defined individual subjects as responders if they developed a two-fold or greater increase in serotype-specific IgG for at least one of the two serotypes. Based on results from an earlier study, low responders were defined as a two-fold increase in serotype-specific IgG for none of the four serotypes at three months post-vaccination.⁸ The responder rate was a percentage of responders who developed a two-fold or greater increase in serotype-specific IgG for at least one of the two serotypes in the BVZV group (group 1) and in the placebo group (group 2).

2.6. Power and statistical analysis

Data were used to conduct a post hoc power analysis (sample size = 25, Type I error probability $\alpha = 0.05$) to calculate the required power per group for detecting relevant changes in the study parameters. Relevant changes were defined as changes necessary for comparing values obtained for 25 people with diabetes who received concomitant administration of PPSV23 and BVZV (group 1) to those for 27 people who received PPSV23 and placebo (group 2). The result was power of 0.97.

For comparison, IgG GMCs and the geometric standard deviation of IgG concentrations of group 1 and group 2 were calculated. The 95% confidence intervals (CI) for the GMCs and the GMCR were computed using a two-sided test with Student's *t* distribution. We inferred significance of results for which $P < .05$. For comparison, differences of responder rates between in BVZV group (group 1) and in the placebo group (group 2) were assessed using Bowker's test. We inferred significance of results for which $P < .05$. Software (R ver.3.2.3; The R Foundation) was used to calculate the *P* values.

3. Results

3.1. Participant characteristics

Of 62 eligible participants, 54 were enrolled into the study: 27 were assigned randomly to group 1; 27 were assigned to group 2. The mean ages at enrollment were 66.7 years for group 1 and 65.8 years for group 2. The mean HbA1c % National Glycohemoglobin Standardization Program (NGSP) and HbA1c International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) at enrollment were 7.29 and 56.61 for group 1, and 7.16 and 55.21 for group 2, respectively. During follow-up, one patient was unable to visit the hospital. Another patient in group 1 died of acute cardiac insufficiency that was unrelated to the vaccination. Consequently, 25 group 1 participants, including 13 (56.5%) women, and 27 group 2 participants, including 10 (43.5%) women, completed the study (Table 1). Additional details were presented in an earlier report.⁵

3.2. Serotype-specific IgG concentrations

Serotypes 6B and 23F were chosen because isolates with these serotypes were found to be drug-resistant and prevalent in adults before implementation of childhood routine immunization of pneumococcal conjugate vaccine in 2013.⁹ Samples collected before and three months after vaccination were stored at -80°C . The antibody concentrations were measured after thawing. Data for the GMCs and the GMCR of serotype-specific IgGs in group 1 with concomitant administration of BVZV and PPSV23 and those in group 2 with concomitant administration of placebo and PPSV23 before and three months after vaccination

Table 1
Baseline patient demographic and clinical characteristics.

	Group 1 PPV23 + Zoster vaccine	Group 2 PPV23 + Placebo	All participants
No. participants	25	27	52
Age (yr)	66.7 ± 4.8	65.8 ± 4.2	66.2 ± 4.5
Female sex—no. (%)	13 (56.5)	10 (43.5)	23 (44.2)
Mean HbA1c%NGSP	7.23 ± 0.61	7.16 ± 1.05	7.19 ± 0.86
Mean HbA1c IFCC (mmol/mol)	55.94 ± 6.67	55.21 ± 11.44	55.56 ± 9.37
Type 1/type 2 diabetes	1/24	2/25	3/49
History of pneumococcal disease	0	0	0

Data are represented as mean ± standard deviation (SD).
NGSP: National Glycohemoglobin Standardization Program.
IFCC: International Federation of Clinical Chemistry and Laboratory Medicine.

are presented in Table 2. The 1.762 GMCR of serotype-specific IgG responses for 6B antigen in group 1 was reduced compared to group 2 with 2.385. The results were not significant ($P = .055$). For the 6B serotype in GMCR for anti-6B IgG responses, there was a 24.00% response rate in group 1 compared with a 48.15% response rate in group 2 ($P = .090$) (Table 2). For antibody response to the 23F serotype, percent response rates were 60.00% in group 1 and 77.78% in group 2. The rate in group 1 was lower than that in group 2, but the difference was not statistically significant ($=0.232$) (Table 2).

3.3. Comparison of responses to serotype-specific 6B and 23F antigens

To understand these data better, we compared pre-antibody and post-antibody titers for individual subjects. Fig. 1 presents line graphs of pre-antibody and post-antibody titers for individual subjects with an additional dotted line at the GMCs, for group 1 and group 2, showing responses for serotypes 6B and 23F. Overall responses for 6B were lower than those for 23F in each group (Fig. 1).

3.4. Correlation between immune responses to pneumococcal polysaccharide antigen and responses to BVZV (immune adherence hemagglutination (IAHA) titers to VZV and skin test responses)

To investigate mechanisms contributing to the lower responses observed against 6B antibodies than those for 23F, we attempted to determine the levels of antigen in each individual. We evaluated cell mediated immunity using the VZV skin test in the recent study. The mean skin test score change, which is the skin test score at 3 months after vaccination minus the score before immunization, was compared.⁵ Comparisons of responses to BVZV from our earlier study to responses

to PPSV23 antigens 6B and 23F are shown in Fig. 2. Neither high responders nor low responders to both BVZV and PPSV23 were observed. No significant correlation was found between immune responses for serotype 6B and 23F of pneumococcal polysaccharide antigens and cellular and humoral immune responses to VZV (Fig. 2).

3.5. Responder rate

The number of high and low responders (responder rates) were 17 (68.0%) and 23 (85.18%) respectively (Table 3). No significant difference was found in the mean fold increase for 6B between responders in group 1 and those in group 2 ($P = .304$). Mean fold increases for 23F antigen were 3.55 in group 1 and 3.78 in group 2, of which both were greater than two-fold. No statistically significant difference was found ($P = .764$). We used Bowker's test for analysis of responder rates to assess changes in the categorical responses taken from subjects before and after vaccination. Statistical significance was found between the 68% responder rate in group 1 and the 85% rate in group 2 ($P = .007$) (Table 3).

4. Discussion

Results of the recent double-blind randomized controlled study to assess the immunity and safety of live BVZV demonstrated that cellular and humoral responses to VZV at 3 months after vaccination were low in elderly patients with diabetes mellitus. We conducted this post-hoc study to assess immunogenicity against PPSV23 under simultaneous vaccination with BVZV or placebo. Participants with diabetes were administered PPSV23 simultaneously with BVZV or placebo. Pneumococcal 6B and 23F serotype-specific IgG antibodies concentrations were measured and evaluated for immunogenicity to PPSV23. Concomitant vaccination with BVZV altered the responses to serospecific antigens 6B and 23F of the PPSV23 in people with diabetes.

One report described that concomitant administration of ZOSTAVAX® (zoster vaccine) did not affect response to PPSV23 for serotypes 3, 14, 19A, and 22F in subjects ≥60 years old.¹⁰ Antibody responses to PPSV23 for serotypes 6B and 23F had not been examined.¹⁰ In this post-hoc study, differences observed with respect to 6B and 23F were found. The results of this study showed that the GMCR of serotype-specific antibody responses for 6B antigen in the BVZV group was reduced compared to the placebo group ($P = .055$). Although a trend was apparent for lower response for serotype 6B antigen in the BVZV group than in the placebo group (Fig. 1), no significant difference between the BVZV group and the placebo group was found in the GMCR ($P = .055$) (Table 2). No statistically significant difference between in the BVZV group and in the placebo group was found for the response rate for 6B ($P = .090$). These results might be attributable to a lack of power of the design. Furthermore, we demonstrated that simultaneous

Table 2
Correlation of immune responses to pneumococcal polysaccharide antigen 6B and 23 F measured using ELISA.

Serotype		Group 1 Varicella zoster vaccine n = 25	Group 2 placebo n = 27	P values between treatment groups (BVZ vaccine vs. placebo)
6B	Before GMC	1.626 (1.499, 1.755)	1.368 (1.269, 1.468)	0.308
	After 3 months GMC	2.866 (1.683, 4.050)	3.134 (2.964, 3.305)	0.667
	GMC	1.762 (0.581, 5.341)	2.385 (0.528, 10.764)	0.055
	Response rate %	24.00	48.15	0.090
23F	Before GMC	2.307 (2.158, 2.456)	1.862 (1.748, 1.977)	0.390
	After 3 months GMC	5.863 (5.617, 6.109)	5.973 (5.850, 6.095)	0.211
	GMC	2.541 (0.565, 11.433)	3.341 (0.840, 12.922)	0.424
	Response rate %	60.00	77.78	0.232

Antibody values are IgG geometric mean concentrations (GMCs) (µg/ml), expressed as the mean (95% confidence interval (CI)).
Geometric mean concentration ratios (GMCRs) are geometric mean of individual concentration ratios (post-vaccination value to pre-vaccination value ratios).
Response rates are percentages of patients with a positive antibody response.
A positive antibody response was defined as a two-fold or greater increase in the IgG concentration.
Fisher's exact test is more accurate than the chi-square test of independence when the expected numbers are small.
We used Fisher's exact test for our datasets of response rate%. We used t-test for analyses other than analysis for the response rate.

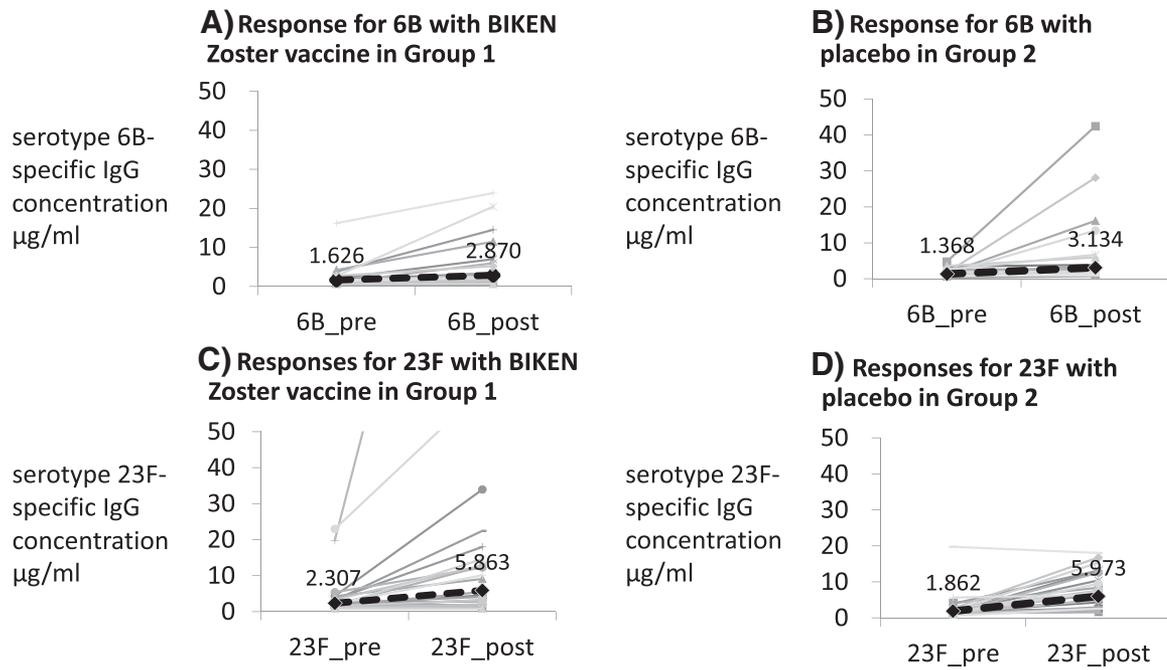


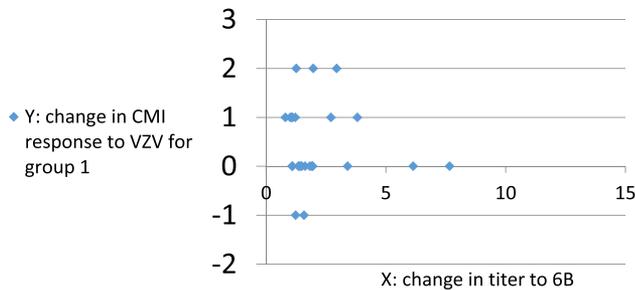
Fig. 1. Antibody response: A, to 6B with BIKEN Zoster vaccine in Group 1; B, to 6B with placebo in Group 2; C, to 23F with BIKEN Zoster vaccine in Group 1; D, to 23F with placebo in Group 2. ◆ - - - ◆ Additional line shows the geometric mean concentrations (GMCs).

administration of BVZV significantly decreased the rate of responders for one of two serotype-specific IgGs for 6B and 23F of PPSV23 compared to the rate with placebo. We observed a 68% responder rate in this study among patients who had developed increases of at least two-fold IgG levels for one of 6B and 23F three months after concurrent vaccination. This rate was significantly lower than the 85% responder

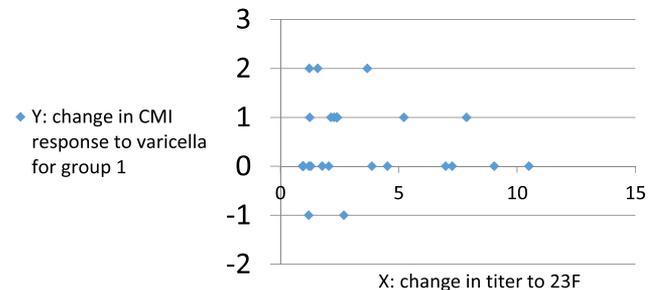
rate at three months after single PPSV23 vaccination in patients with diabetes (Table 3).

Increased susceptibility to infectious diseases in people with diabetes is reportedly attributable to defects in both humoral and cell-mediated immunity. One earlier report described that responses to pneumococcal antigens were impaired in patients with diabetes.¹¹ It is

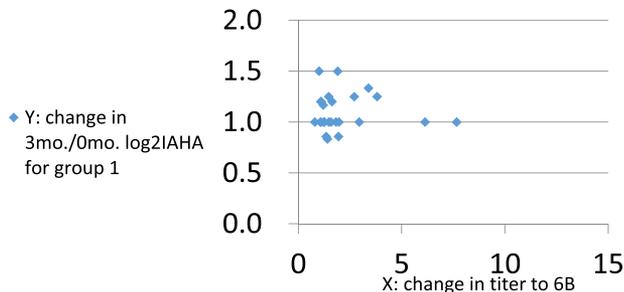
A) change in titer to 6B/ change in skin test response to BIKEN zoster vaccine



B) change in titer to 23F/ change in skin test response to BIKEN zoster virus



C) change in titer to 6B/ change in IAHA response to varicella zoster virus



D) change in titer to 23F/ change in IAHA response to varicella zoster virus

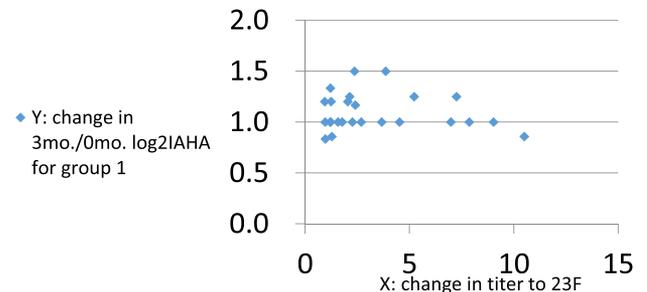


Fig. 2. Data from an earlier study were used.⁵ Figures show that the x-axis is changed in titer to 6B (panels A and C) or 23 F (panels B and D) and that the y-axis is changed in response to varicella zoster virus for group 1 (BVZV vaccine group). Fig. 2A and B Y show changes in cell mediated immunity (CMI) response to varicella zoster virus for group 1: skin test response. Fig. 2C and D Y shows changes in humoral immunity (antibody) response to varicella zoster virus for group 1: immune adherence hemagglutination (IAHA) titer.

Table 3

Comparison of responders to pneumococcal polysaccharide antigen 6B and 23F in BVZV group and placebo group.

	Group 1 <i>n</i> = 25 Varicella zoster vaccine number	Group 1 Varicella zoster vaccine the mean (95% confidence interval (CI)).	Group 2 <i>n</i> = 27 placebo number	Group 1 placebo the mean (95% confidence interval (CI)).	<i>P</i> values between treatment groups (BVZ vaccine vs. placebo)
Responder: 6B or 23F post/pre > or = 2	17		23		
Responder: 6B ratio post/pre		1.94 (0.54, 6.93)		2.48 (0.53, 11.56)	0.304
Responder: 23F ratio post/pre		3.55 (0.86, 14.05)		3.78 (1.16, 12.33)	0.764
Low Responder: both of 6B and 23F post/pre < 2	8		4		
Responder rate %	68.00		85.19		0.007

Responder rates are percentages of responders who developed a two-fold increase in serotype-specific IgG for at least one of the two serotypes in each group. We used Bowker's test for analysis of the responder rate to evaluate changes in categorical responses taken from participants before and after vaccination.

usually regarded as an enhancement of immunogenicity when the antibody concentration rises more than two-fold by the PPSV23 vaccination. In this study, for 21 of 27 patients in the placebo group and 15 of 25 patients in the BVZV group, antibodies against 23F serotype were elevated to more than double those before PPSV23 vaccination. Furthermore, in 14 of 27 patients in the placebo group and 6 of 25 patients in the BVZV group, antibodies against 6B serotype were elevated to more than double those before PPSV23 vaccination. Although no significant difference was found in fold increases between the groups, a moderate fold increase in IgG for serotype 6B was found. Moreover, a much larger fold increase in IgG for serotype 23F was found three months after vaccination (Fig. 1).

We observed that 68% of responders in the BVZV group and 85% of those in the placebo group had developed increases of two-fold or greater in IgG levels for 6B or 23F three months after concurrent vaccination of PPSV23. A significant difference was found between the groups ($P = .007$). The 68% responder rate found in the BVZV group was as low as the 69% responder rate one month after single PPSV23 vaccination in patients with chronic obstructive pulmonary diseases observed by other researchers.⁸ However, an exact comparison this cannot be made because of differences in measurement methods and the points of blood sampling.

The BVZV we used to prevent herpes zoster (HZ) contained approximately 50,000 plaque-forming units per dose derived from the same Oka strain-derived vaccine, equivalent to Zostavax® zoster vaccine, containing a similar mean titer of 42,000–67,000 plaque forming units per dose.¹² This BVZV we used was approved for prevention of HZ in Japan on March 18, 2016.¹³ No guidelines have been issued in Japan regarding refraining from simultaneous immunization of PPSV23 and PVZV in elderly or diabetic subjects. In addition to the results reported herein for this post-hoc study, results reported for the recent double-blind randomized controlled study showed that BVZV did not boost VZV antibody responses and CMI against VZV in elderly patients with diabetes under concomitant administration with PPSV23.⁵ We demonstrated earlier that VZV antibody and VZV-specific CMI responses were activated by live BVZV without concomitant PPSV23 administration in elderly patients with diabetes, just as in healthy individuals.⁴ These findings constitute direct evidence that concomitant administration of pneumococcal vaccine and BVZV can diminish the protective effects of PPSV23 and BVZV.

We recommend that BVZV and PPSV23 be given separately, at least in people with diabetes, because simultaneous vaccination might alter immune responses. However, it is advocated that the vaccines should be given simultaneously to avoid a missed opportunity to vaccinate against herpes zoster and invasive pneumococcal disease because no direct evidence shows that simultaneous administration of zoster vaccine and PPSV23 presents an increased risk of these two diseases.¹⁴ The Centers for Disease Control and Prevention advocated concomitant administration of zoster vaccine Zostavax® and PPSV23 to avoid missing opportunities to vaccinate against HZ and pneumococcal disease.¹⁵ Simultaneous vaccination of zoster vaccine and trivalent inactivated influenza vaccine in a double-blind, controlled sub-study revealed that 374

elderly adults had no impaired immune response.¹⁶ By contrast, a double-blind, controlled clinical trial of 473 elderly people randomized to receive Zostavax® and PPSV23 simultaneously, or PPSV23 alone followed 4 weeks later by Zostavax® alone, elicited the following results. Four weeks after vaccination, VZV antibody levels of subjects after simultaneous immunization were significantly lower than those after separate immunization.¹⁰ Therefore, the U.S. FDA approved a revision to Zostavax® in December 2009. To avoid a potential decrease in VZV immunogenicity, Zostavax® and PPSV23 should not be given concomitantly.¹⁷

A large observational study of community-dwelling elderly people compared the incidence of HZ between 7187 persons who were concomitantly vaccinated and 7179 persons who were nonconcomitantly vaccinated with PPSV23 and Zostavax® during 2.75 years. No evidence of increased risk of HZ infection in the population receiving Zostavax® and PPSV23 concomitantly was found. At present, drug interactions are described in a Zostavax® package insert advising that administration of the two vaccines be separated by at least 4 weeks.¹⁶ A rapid decline in Zostavax® effectiveness was reported recently, from 68.7% in the first year to 4.2% in the eighth year in 176,078 elderly individuals 60 years old or older who had been vaccinated with HZ vaccine.¹⁸ Results of our earlier study suggest a shorter duration of BVZV effectiveness in people with concurrent immunization of BVZV and PPSV23 than in people with separate immunization. No significant difference in the incidence was found between populations administered Zostavax® concomitantly and nonconcomitantly with PPSV23 during the 2.75 years. However, differences between them were found over a longer observational period. Future studies should investigate whether the decline in zoster vaccine effectiveness is attributable to concomitant immunization. These results might not engender the same statement that the efficacy of simultaneous immunization of Zostavax® and PPSV23 is equal to that of separate immunization based on an epidemiological study conducted by the CDC over approximately three years.

This post hoc analysis has several limitations. Firstly, this post-study analysis was not designed to confirm differences in antibody titers between groups. IgG antibodies specific for more serotypes in sera should be evaluated, but limited amounts of sera were stored. Secondly, BVZV is not necessarily equivalent to the Oka-Merck strain zoster vaccine (Zostavax®) licensed in dozens of countries. Few reports describe studies examining lower responses to zoster vaccine (Zostavax®) in concurrent immunization than in separate immunization.¹⁰ Zostavax® was derived from the original Biken Oka strain but such equivalence has not been demonstrated for BVZV. Once it is recommended, further large-scale studies to assess concurrent immunization effects will be difficult to conduct. Thirdly, these assessments of CMI or humoral immunity are of limited clinical significance when correlates of actual immunity against disease outcomes have not been established.

Post-hoc analysis results have demonstrated that concurrent immunization of BVZV and PPSV23 might alter the immunogenicity of PPSV23. Results show that PPSV23 might be less immunogenic with concurrent immunization of BVZV than with concurrent administration of placebo in elderly people with diabetes. We demonstrated that

pneumococcal antibody titer was enhanced irrespective of immunization of BVZV, but with a lower responder rate. In conclusion, taken together with findings from a previously published study,⁵ our results demonstrate that immune responses to pneumococcal vaccine can be altered by simultaneous immunization of BVZV, which is presumed to be of scientific importance.

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