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Prophylactic vaccination with a live-attenuated herpes zoster vaccine in lung transplant candidates

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KEYWORDS:
lung transplantation;
herpes zoster;
HZ vaccine;
vaccination;
prophylactic

BACKGROUND: Herpes zoster (HZ) is caused by the reactivation of varicella−zoster virus (VZV). Patients with lung transplants are at high risk for HZ owing to their immunocompromised status and the need for lifelong immunosuppression. In this study, patients on the waiting list for lung transplantation were vaccinated by a live-attenuated HZ vaccine (Zostavax, Merck Sharp & Dohme), and the safety and immunogenicity of this vaccine were studied.

METHODS: In total, 105 patients with end-stage pulmonary disease (ESPD) were enrolled (68 participants received 1 dose of Zostavax and 37 participants were enrolled as unvaccinated controls). Among them, 43 patients underwent lung transplantation and were followed up for further analysis. VZV immunoglobulin G antibody titers and VZV-specific cell-mediated immunity (CMI) on multiple time points before and after vaccination and before and after transplantation were measured.

RESULTS: Immune response to Zostavax was higher in younger patients, highest within 3 months after vaccination, and not influenced by gender or type of ESPD. Age, cytomegalovirus serostatus, and immunity to VZV at baseline impacted the subsequent immune response to the vaccine. Short-term immunosuppressant treatment had strong effects on VZV CMI levels, which returned to a high level at 6 months after transplantation in vaccinated patients. Zostavax did not impact infection or rejection rate after transplantation.

CONCLUSIONS: Zostavax was safe and induced a robust humoral and cellular response for patients awaiting lung transplantation regardless of the type of ESPD. Patients younger than the recommended vaccination age of over 50 years showed a strong response and could also benefit from pre-transplant immunization.

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Varicella−zoster virus (VZV) establishes a lifelong latency after primary infection (chickenpox). Reactivation of VZV leads to herpes zoster (HZ), with symptoms such as painful unilateral vesicular rash, itching, and headache.[1] Although the eruption of skin resolves within 2 to 4 weeks, complications such as post-herpetic neuralgia (PHN) frequently occur after HZ.[2] Aging is an important risk factor for HZ, and the incidence of HZ as well as that of PHN increase with age.[3]

The frequency of VZV-specific T cells decreases with age, whereas VZV-specific antibodies remain at stable

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levels. Therefore, cell-mediated immunity (CMI) to VZV rather than VZV-specific antibodies is considered to play a key role in preventing VZV reactivation.[4–6] Solid organ transplant recipients with decreased CMI due to immunosuppressive treatment are at up to 9 times higher risk for HZ than healthy individuals.[7] Lung transplantation is an established treatment for end-stage pulmonary disease (ESPD). The proportion of elderly lung transplant recipients keeps increasing in recent years.[8–10] The incidence of HZ among lung transplant recipients is higher than among the recipients of other types of transplants, between 11.6% and 14.3%,[11–13] which could be the consequence of continuous immunosuppression at high dose and age at transplantation.[1,14]

Although anti-viral treatments are available for HZ, the prevention of HZ by vaccination could be important in patients with transplants who face a higher risk for HZ and severe complications. Solid organ transplant candidates are preferably immunized while they are awaiting transplantation.[15] A live-attenuated HZ vaccine (Zostavax, Merck Sharp & Dohme) was approved by the Food and Drug Administration in 2006.[16] Because of its live-attenuated feature, this vaccine is contraindicated for immunocompromised patients.[17] Until recently, limited studies are conducted regarding the usage of Zostavax before transplantation. Miller et al[18] performed a pilot study in which 34 subjects received the HZ vaccine at least 30 days before kidney transplantation. Although there was a small number of participants, the study showed that Zostavax was safe and induced significant humoral immune response to VZV in patients with end-stage renal disease awaiting transplantation. In this study, we conducted a pre-transplant vaccination study to evaluate the safety, efficiency, and immunogenicity of Zostavax among patients with ESPD before and after lung transplantation.

Methods

Study design and participants

HZ vaccination was started at the University Medical Center Groningen, The Netherlands, in November 2016. All patients who were newly screened for lung transplantation were given 1 dose of Zostavax. Blood was drawn from vaccinated patients aged ≥18 years who were willing to participate in this study before and after vaccination (Figure 1). Patients who were already on the waiting list but did not receive the HZ vaccine were considered eligible to participate in this study as controls, and blood was drawn once. When these 2 groups of patients had undergone lung transplantation, blood was drawn following the post-transplant scheme (Figure 1). Serum and peripheral blood mononuclear cells (PBMCs) were isolated from freshly collected blood and then stored at −20°C and in liquid nitrogen, respectively. The study protocol was reviewed and approved by the institutional review board of the University Medical Center Groningen (METc 2016/090). Written consent was obtained from all the participants at enrollment.

Assessment of humoral immune response to HZ vaccination

The humoral immune response to HZ vaccination was evaluated by an in-house glycoprotein (gp) VZV enzyme-linked immunosorbent assay as previously described.[19] VZV-purified gps (EastCoast Bio) and pooled human serum with known levels of anti-gpVZV were used as antigen and standard, respectively. According to the recommendations of Institut Virion/Serion, positive VZV IgG levels were higher than 100 mIU/ml.

Assessment of cellular immune response to HZ vaccination

The VZV-specific CMI to HZ vaccination was studied by an interferon (IFN)-γ enzyme-linked immunospot (ELISpot) assay as previously described.[19] Briefly, 2×10^5 per well PBMCs suspension were stimulated for 48 hours with 10 μl 1:14 prediluted ultraviolet-inactivated Zostavax (>19,400 plaque-forming unit/0.65 ml), 5 μg/ml concanavalin A (positive control), or only culture medium (negative control). All samples were measured in duplicate except for the positive control. After incubation, staining, and drying of the plates, spots were counted using an AID ELISpot Reader (Autoimmun Diagnostika GmbH). Spots of negative control wells were subtracted from corresponding stimulated wells. The number of spots represented the number of IFN-γ–secreting cells per 2×10^5 PBMCs (spot-forming cells [SFCs]).

Statistical analyses

Data of vaccinated and unvaccinated patients were compared using Mann–Whitney test. To compare results within a group between baseline and subsequent time points of after vaccination and after transplantation of humoral/cellular response to HZ vaccination, Wilcoxon signed-rank test was used.

To analyze the effect of predictor variables on VZV IgG or VZV SFCs levels after vaccination before transplantation, we

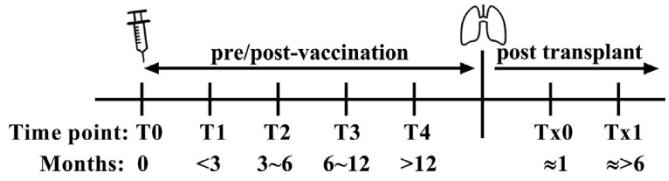

Figure 1 Time schedule for blood withdrawal. Newly screened lung transplant candidates received 1 dose of Zostavax at T0. Patients already on the waiting list were included at regular outpatient visits (T0). Blood was drawn at T1, T2, T3, T4. Once patients received a lung transplant, blood was drawn at Tx0 and Tx1. None of the patients were lost to follow-up, but some samples could not be obtained owing to logistical reasons, and the total numbers of time points varied among patients. T0, baseline; T1, <3 months after vaccination; T2, between 3 and 6 months after vaccination; T3, between 6 and 12 months after vaccination; T4, >12 months after vaccination; Tx0, 1 month after transplantation; Tx1, 6 months or longer after transplantation.

conducted a 2-level, multilevel analysis. The VZV IgG or VZV SFCs levels were the dependent variables, and potential predictors were gender, baseline age, time (baseline [T0], <3 months after vaccination [T1], between 3 and 6 months after vaccination [T2], between 6 and 12 months after vaccination [T3], and >12 months after vaccination [T4]), VZV IgG or VZV SFCs at baseline, cytomegalovirus (CMV) status, and ESPD (as described in Table 1). These predictor variables were included on the patient level (Level 1), which was allowed to interact with the random intercepts and slopes estimated from the repeated measurements (Level 2; T0–T4 as shown in Figure 1) after vaccination. Variables were entered 1 by 1 in the multilevel analysis model and remained in this model if the estimated regression coefficient (b) was significant or the model fit of the regression equation improved significantly according to the −2 log-likelihood criterion. Interaction between predictors was explored when the main effects were significant. Data of all participants were used in this analysis. Residuals were checked for

Table 1 Characteristics of the Participants

Characteristic	All enrolled patients N = 105			Transplant patients $n = 43$[a]		
	Vaccinated	Unvaccinated	p-value	Vaccinated	Unvaccinated	p-value
Number of patients, n (%)	68 (64.8)	37 (35.2)		29 (67.4)	14 (32.6)	
Baseline age, years						
Median (range)	57.1 (19.1–66.7)	57.6 (19.2–70.0)	0.445	54.4 (19.1–66.6)	59.2 (35.5–68.4)	0.040[b]
Gender, n (%)						
Male	34 (50.0)	13 (35.1)	0.157	20 (69.0)	8 (57.1)	0.507
Female	34 (50.0)	24 (64.9)		9 (31.0)	6 (42.9)	
ESPD, n (%)						
Chronic obstructive pulmonary disease/emphysema	38 (55.9)	20 (54.1)	>0.999	12 (41.4)	9 (64.3)	0.203
α_1-Antitrypsin deficiency	8 (11.8)	3 (8.1)	0.743	4 (13.8)	2 (14.3)	>0.999
Pulmonary fibrosis/interstitial lung disease	8 (11.8)	3 (8.1)	0.743	7 (24.1)	1 (7.1)	0.240
Pulmonary arterial hypertension	9 (13.2)	5 (13.5)	>0.999	2 (6.9)	1 (7.1)	>0.999
Cystic fibrosis/bronchiectasis	5 (7.4)	6 (16.2)	0.189	4 (13.8)	1 (7.1)	>0.999
Baseline CMV serostatus, n (%)						
+	42 (61.8)	19 (51.4)	0.310	14 (48.3)	8 (57.1)	0.747
−	26 (38.2)	18 (48.6)		15 (51.7)	6 (42.9)	
Age at vaccination, years, n (%)						
≤50	16 (23.5)	7 (18.9)	0.631	10 (34.5)	1 (7.1)	0.071
50–60	30 (44.1)	16 (43.2)	>0.999	10 (34.5)	7 (50.0)	0.507
>60	22 (32.4)	14 (37.8)	0.668	9 (31.0)	6 (42.9)	0.507
Age at transplantation, years						
Median (range)	—	—	—	54.5(19.9–66.9)	59.9 (37.4–68.9)	0.039[b]
Follow-up time after T0, months						
Median (range)	21.5 (7.0–34.5)	26.5 (2.7–33.8)	0.035[b]	24.0 (13.9–34.5)	29.4 (9.0–33.8)	0.025[b]
Follow-up time after transplantation, months						
Median (range)	—	—	—	16.6 (2.7–27.9)	11.6 (2.5–30.6)	0.255
D/R CMV serostatus, n (%)						
D+/R+	—	—	—	6 (20.7)	6 (42.9)	0.160
D+/R−	—	—	—	5 (17.2)	3 (21.4)	>0.999
D−/R+	—	—	—	8 (27.6)	2 (14.3)	0.456
D−/R−	—	—	—	10 (34.5)	3 (21.4)	0.491
Acute rejection, n (%)						
Yes	—	—	—	11 (37.9)	3 (21.4)	0.324
No	—	—	—	18 (62.1)	11 (78.6)	
Infections, n (%)						
Bacterial	—	—	—	21 (72.4)	7 (50.0)	0.184
Fungal	—	—	—	7 (24.1)	4 (28.6)	>0.999
Viral (except HZ)	—	—	—	6 (20.7)	2 (14.3)	>0.999
HZ	—	—	—	1 (3.4)	2 (14.3)	0.243
No infection	—	—	—	6 (20.7)	4 (28.6)	0.704

Abbreviations: CMV, cytomegalovirus; D, donor; ESPD, end-stage pulmonary disease; HZ, herpes zoster; R, recipient; T0, baseline.
p-values are displayed between groups. Fisher's exact test was used to compare factors.
[a]All the patients underwent bilateral lung transplantation except 1 vaccinated patient who underwent liver–lung transplantation.
[b] Significant p-value

a normal distribution. After the natural logarithmic (ln) transformation of VZV IgG and VZV SFCs, residuals were normally distributed.

A 2-tailed p-value < 0.05 was regarded as statistical significance. All data were analyzed using Prism 7 for Windows (GraphPad Software, Inc.) and SPSS Statistics (version 23, IBM).

Results

Patient's characteristics

In total, 105 patients with ESPD were included in this study between November 2016 and November 2019. A total of 68 patients received 1 dose of HZ vaccine, and 37 patients were enrolled as unvaccinated controls. Of these, 46 underwent lung transplantation, but 3 patients died at 0.3, 1.5, and 3.9 months after transplantation and could not be included for further investigation. Thus, we studied immunogenicity after transplantation in 43 patients (29 vaccinated and 14 unvaccinated) (Figure 2).

Age at baseline was similar between the groups, but unvaccinated patients who underwent transplantation were older than vaccinated patients who underwent transplantation (Table 1). The percentage of female patients was significantly higher in unvaccinated patients (64.9%), but more male patients underwent lung transplantation in both groups. Chronic obstructive pulmonary disease/emphysema was the primary ESPD for waiting list patients as well as patients who underwent transplantation.

Patients who underwent transplantation had quadruple immunosuppression consisting of basiliximab at Days 1 and 5 and maintenance therapy with tacrolimus, mycophenolate mofetil (MMF), and prednisolone. Methylprednisolone was given at 125 mg 3 times a day in the first 24 hours, then prednisolone was given for 7 days at 0.4 mg/kg, then at 0.2 mg/kg until Day 90, and thereafter, 0.1 mg/kg. MMF dose remained unchanged at 1,000 mg twice a day, started at transplantation, and tacrolimus was started intravenously at a target trough level of 15 mg/liter and tapered to a maintenance trough level of 6 to 9 mg/liter after Day 90. A total of 1 vaccinated patient and 1 unvaccinated patient switched from MMF to azathioprine owing to side effects. The median interval between vaccination and transplantation was 7.8 months, with a range from 0.7 to 26.6 months. The median follow-up after lung transplantation was 16.6 months in vaccinated patients and 11.6 months in unvaccinated patients ($p = 0.255$). It is important to note that patients with CMV who received grafts from CMV− or CMV+ donors were treated with anti-viral prophylaxis (3 months of valaciclovir and 1 year of valganciclovir, respectively). CMV+ recipients received 3 months of

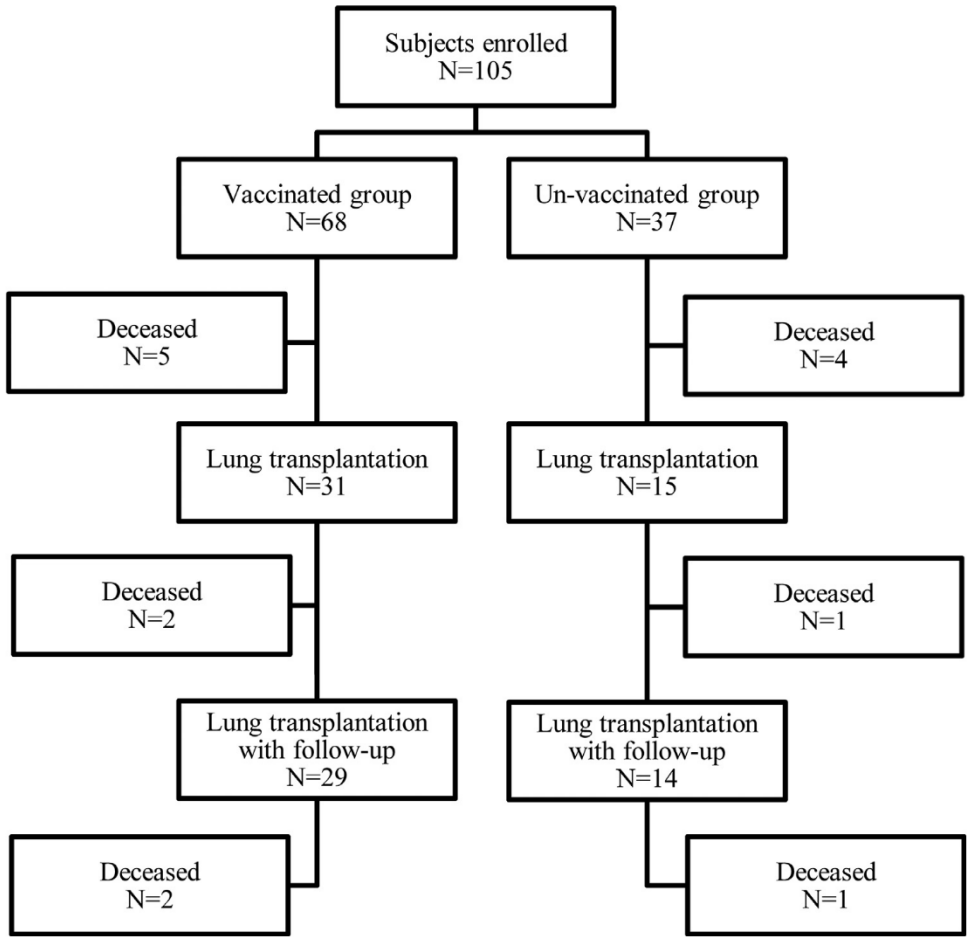

Figure 2 Flow chart of participants.

valganciclovir prophylaxis. Most patients (62.1% vaccinated, 78.6% unvaccinated patients) did not experience rejection during this period, but many patients experienced infections after transplantation. Among them, bacterial infection was the most common infection. Patients with rejection were treated with 1 g of methylprednisolone for 3 days. There were no statistically significant differences in rejection and infection between vaccinated and unvaccinated patients ($p = 0.324$ and $p = 0.704$).

Humoral immune response to HZ vaccine

All participants were VZV seropositive at the time of enrollment in the study. Figure 3a displays the anti-gpVZV IgG levels before the transplantation of vaccinated patients and controls. No patient was lost to follow-up, but owing to logistic reasons, blood samples could not be collected at all the 5 time points (T0, <3, 3−6, 6−12, >12 months after vaccination) from every patient. At T0, there was no significant difference ($p = 0.225$) in VZV IgG levels between the vaccinated and unvaccinated groups. The highest VZV IgG geometric mean concentrations were detected (3,597.3 mIU/ml) within 3 months after HZ vaccination, with 2.86 (95% CI: 2.11−3.89, $p < 0.001$) geometric mean fold rises (GMFRs) compared with that at T0. From 3 months to 1 year after the HZ vaccination, VZV IgG levels decreased but were still significantly higher than those at the baseline. Vaccinated patients were stratified according to age, CMV status, and VZV IgG titers at baseline (Figure 3b−d). Within 3 months after vaccination, patients aged ≤50 years showed higher GMFR than older patients (5.71 vs 2.53, $p = 0.002$) (Figure 3b). A higher humoral response was found at 3 months or longer after vaccination in patients who were CMV+ than in patients who were CMV− (Figure 3c). Patients with high pre-vaccination VZV IgG titers stayed at a higher level than patients with low pre-

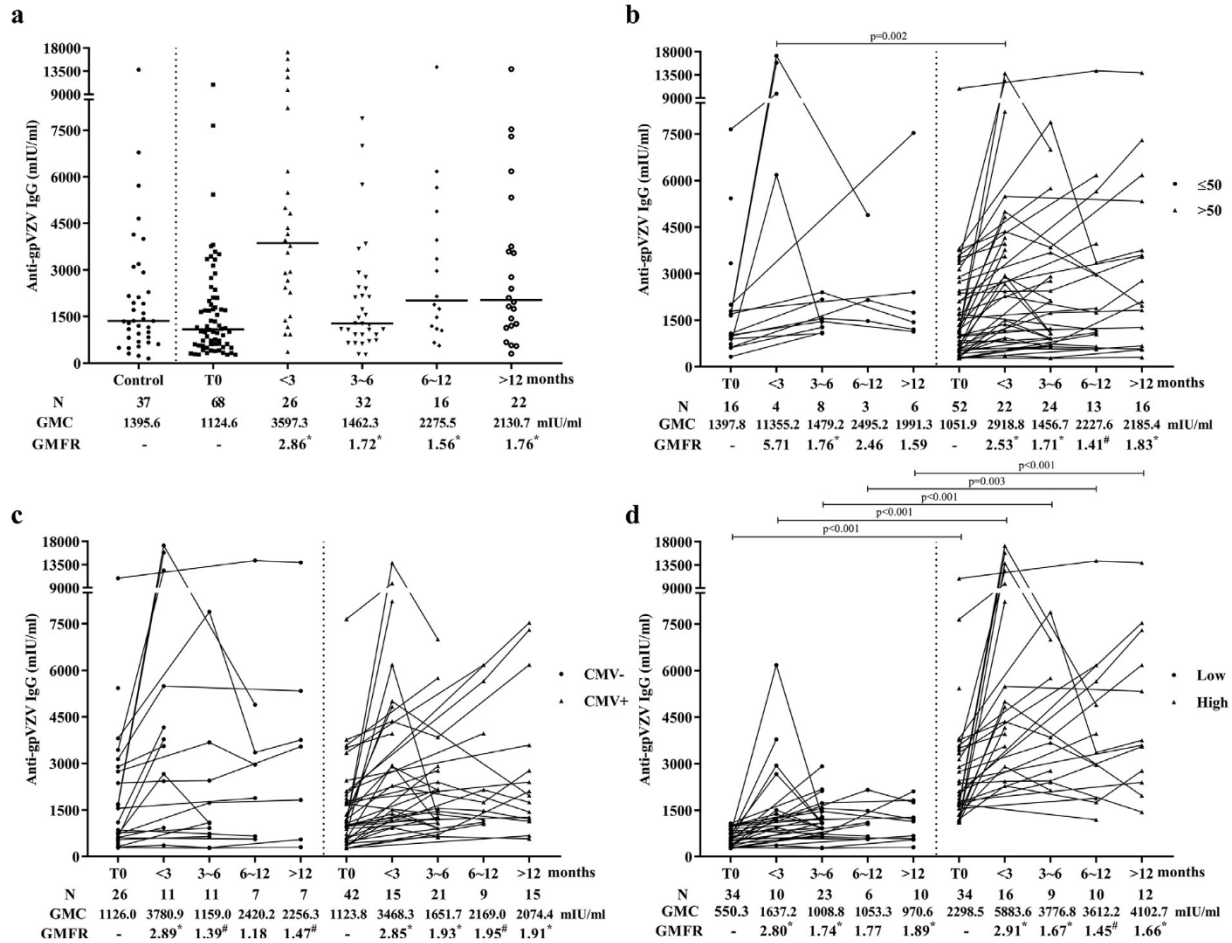

Figure 3 Humoral immunogenicity of the HZ vaccine. (a) Levels of anti-gpVZV IgG antibody in 68 vaccinated patients at T0 and <3 months, between 3 and 6 months, between 6 and 12 months, and more than 12 months after vaccination as well as the baseline levels in 37 unvaccinated patients (control). Horizontal lines show the median. (b) Anti-gpVZV IgG levels of 2 age sub-groups (aged <50 or >50 years at T0) in vaccinated patients at the 5 different time points mentioned earlier. (c) Anti-gpVZV IgG levels in vaccinated patients at the 5 different time points mentioned earlier (patients were divided into CMV− and CMV+ groups according to their CMV status at T0). (d) Anti-gpVZV IgG levels in vaccinated patients at the 5 different time points mentioned earlier (patients were divided into 2 groups according to their baseline VZV IgG levels of higher or lower than the median levels at T0). GMC of every group and GMFR at different time points after vaccination over T0 in vaccinated patients are shown under each figure. *p-value < 0.01 compared with T0. #p-value < 0.05 compared with T0. CMV, cytomegalovirus; GMC, geometric mean concentration; GMFR, geometric mean fold rise; gp, glycoprotein; HZ, herpes zoster; N, number of subjects at different time points or sub-groups; T0, baseline; VZV, varicella−zoster virus.

vaccination VZV IgG titers even at 1 year after vaccination (Figure 3d).

Cellular immune response to HZ vaccine

ELISpot assays were performed in patients who underwent transplantation. The number of VZV SFCs was highest within 3 months after vaccination (81.3 ± 73.9), which then decreased later (Figure 4a). Divisions into different sub-groups were done as for humoral response (Figure 4b −d). A significant increase in VZV SFCs was seen within 3 months in patients aged >50 years ($p = 0.009$) and also in patients with CMV− status ($p = 0.020$) and low baseline levels ($p = 0.014$). Patients who were CMV− showed overall high VZV SFCs at all the 5 time points compared with patients who were CMV+ (Figure 4c). Patients with high baseline VZV SFCs numbers were comparatively high at later time points, whereas patients with low baseline VZV SFCs numbers remained low over time (Figure 4d). There was a correlation between the VZV IgG levels and VZV SFCs levels at T0 and all the time points after vaccination (Spearman rank correlations, $r = 0.409$, $p < 0.001$).

Multilevel analysis of humoral and cellular immune response after vaccination before transplantation in vaccinated patients

Multilevel analysis was performed to identify the predictive factors for the efficacy of vaccination. Data were analyzed after vaccination but before transplantation, and they showed that CMV status, VZV IgG level at baseline, and time significantly predicted VZV IgG levels after vaccination (Table 2). CMV seropositivity showed a positive effect on VZV IgG levels. Gender and ESPD did not contribute significantly to the model fit. VZV IgG levels at T1 were significantly higher than at T0. Higher VZV IgG levels at

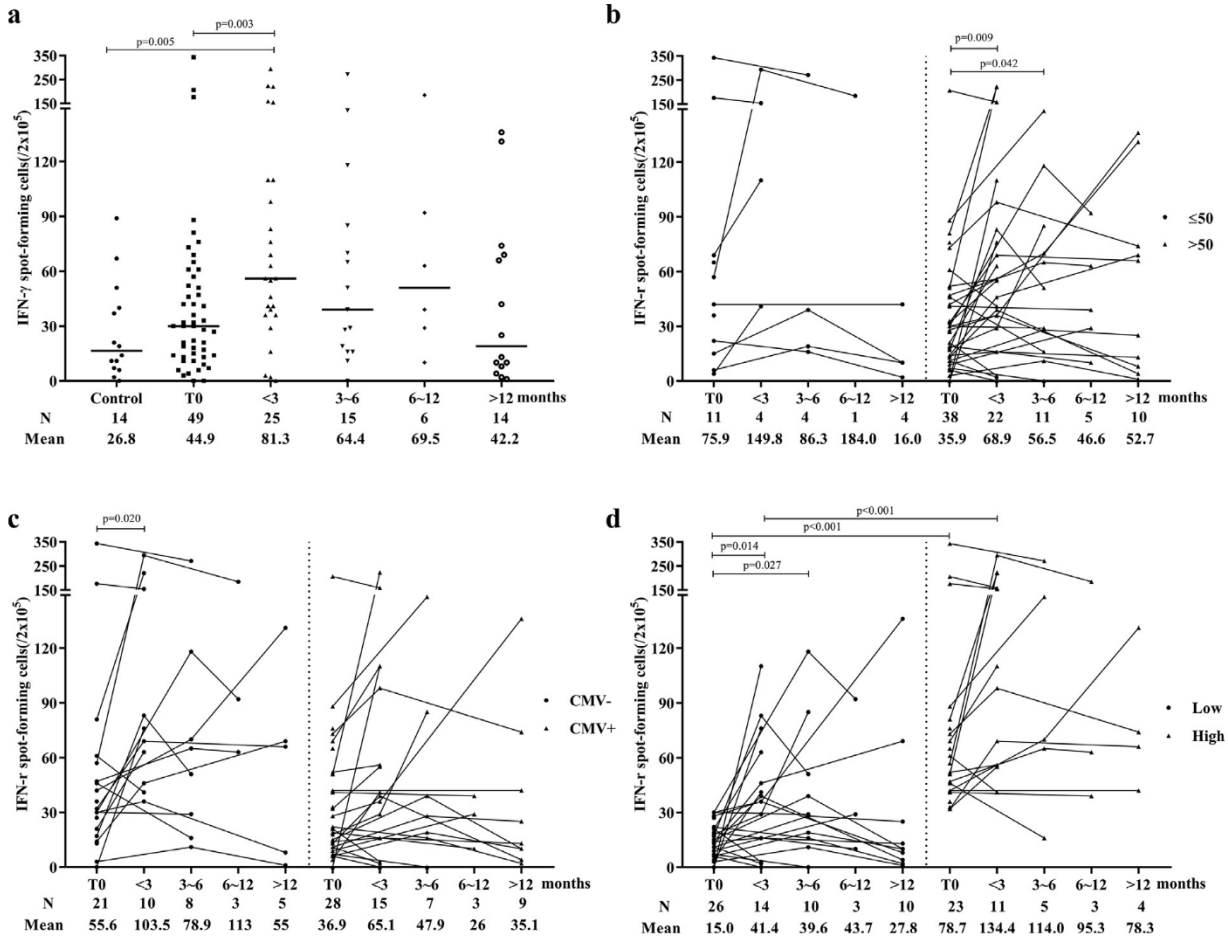

Figure 4 Cellular immunogenicity of the HZ vaccine. (a) The number of VZV-stimulated IFN-γ–secreting T-cells spots at T0 and <3 months, between 3 and 6 months, between 6 and 12 months, and more than 12 months after vaccination as well as the baseline levels of 14 unvaccinated patients (controls). Horizontal lines show the median. (b) The number of VZV-stimulated IFN-γ–secreting T-cells spots of 2 age sub-groups (aged <50 or >50 years) in vaccinated patients at the 5 different time points mentioned earlier. (c) The number of VZV-stimulated IFN-γ–secreting T-cells spots in vaccinated patients at the 5 different time points mentioned earlier (patients were divided into CMV− and CMV+ groups according to their CMV status at T0). (d) The number of VZV-stimulated IFN-−γ secreting T-cells spots in vaccinated patients at the 5 different time points mentioned earlier (patients were divided into 2 groups according to their baseline IFN-γ spots values of higher or lower than the median levels at T0). The mean of the number of IFN-γ–secreting T-cells spots is shown under each figure. CMV, cytomegalovirus; HZ, herpes zoster; IFN, interferon; N, number of subjects at different time points or sub-groups; T0, baseline; VZV, varicella−zoster virus.

Table 2 Results of Multilevel Analysis for Anti-gpVZV IgG Levels With Follow-Up Time After Vaccination as an ln Function

Parameter	Estimate	SE	*p*-value	95% CI	
				Lower bound	Upper bound
Intercept	1.656	0.786	0.037	0.105	3.208
Timing T0	−1.555	0.932	0.097	−3.395	0.284
Timing T1	5.524	1.156	<0.001	3.239	7.808
Timing T2	0.148	1.036	0.887	−1.900	2.195
Timing T3	1.124	1.037	0.281	−0.929	3.176
Age	0.004	0.010	0.701	−0.015	0.023
ln VZV IgG levels at baseline	0.825	0.083	<0.001	0.661	0.988
CMV status (negative)	−0.169	0.071	0.019	−0.309	−0.028
Timing T0* ln VZV IgG levels at baseline[a]	0.174	0.098	0.078	−0.020	0.368
Timing T1* ln VZV IgG levels at baseline[a]	−0.301	0.122	0.015	−0.543	−0.060
Timing T2* ln VZV IgG levels at baseline[a]	−0.007	0.115	0.955	−0.233	0.220
Timing T3* ln VZV IgG levels at baseline[a]	0.027	0.125	0.829	−0.219	0.273
Timing T0* age[a]	−0.004	0.011	0.694	−0.025	0.017
Timing T1* age[a]	−0.052	0.012	<0.001	−0.076	−0.029
Timing T2* age[a]	−0.003	0.013	0.826	−0.029	0.023
Timing T3* age[a]	−0.025	0.013	0.050	−0.050	<−0.001

Abbreviations: CMV, cytomegalovirus; gp, glycoprotein; ln, natural logarithmic; SE, standard error of the regression coefficient; T0, baseline; T1, <3 months after vaccination; T2, between 3 and 6 months after vaccination; T3, between 6 and 12 months after vaccination; T4, >12 months after vaccination; VZV, varicella–zoster virus.

Timing T4, CMV status (positive), Timing T4*ln VZV IgG levels at baseline, and Timing T4 *age were the reference category; *p* = significance of estimated regression coefficient (*b*).

[a]Interaction term of different timepoint and interaction effect of ln VZV IgG levels at baseline or age.

baseline predicted significantly higher VZV IgG levels. Significant interaction effects were found between age and time and between VZV IgG and time in predicting VZV IgG levels.

As for the VZV SFC levels, multilevel analyses showed that CMV status, VZV SFC levels at baseline, and time significantly predicted VZV SFC levels after vaccination (Table 3). CMV seropositivity showed a negative effect on VZV SFCs levels. Gender, age, and ESPD did not contribute significantly to the model fit. VZV SFCs levels at T1 were significantly higher than at T0. Higher VZV SFC baseline levels predicted significantly higher VZV SFC levels. A significant interaction was found between VZV SFCs and time.

Table 3 Results of Multilevel Analysis for VZV-Stimulated IFN-γ–Secreting T-Cells Spots With Follow-Up Time After Vaccination as an ln Function

Parameter	Estimate	SE	*p*-value	95% CI	
				Lower bound	Upper bound
Intercept	−0.466	0.841	0.580	−2.133	1.200
Timing T0	0.413	0.905	0.649	−1.381	2.208
Timing T1	2.941	0.941	0.002	1.077	4.805
Timing T2	1.441	1.038	0.168	−0.617	3.499
Timing T3	1.361	1.947	0.486	−2.498	5.220
CMV status (negative)	0.288	0.138	0.040	0.013	0.563
ln VZV SFCs levels at baseline	1.146	0.268	<0.001	0.616	1.676
Timing T0* ln VZV SFCs levels at baseline[a]	−0.167	0.285	0.558	−0.732	0.397
Timing T1* ln VZV SFCs levels at baseline[a]	−0.734	0.294	0.014	−1.318	−0.151
Timing T2* ln VZV SFCs levels at baseline[a]	−0.373	0.322	0.249	−1.011	0.265
Timing T3* ln VZV SFCs levels at baseline[a]	−0.304	0.572	0.596	−1.437	0.829

Abbreviations: CMV, cytomegalovirus; IFN, interferon; ln, natural logarithmic; SFC, spot-forming cell; T0, baseline; T1, <3 months after vaccination; T2, between 3 and 6 months after vaccination; T3, between 6 and 12 months after vaccination; T4, >12 months after vaccination; VZV, varicella–zoster virus.

Timing T4, CMV status (positive), and Timing T4*ln VZV–SFCs levels at baseline were the reference category; *p* = significance of estimated regression coefficient (*b*).

[a]Interaction term of different timepoint and interaction effect of ln VZV–SFCs levels at baseline.

Immunogenicity of HZ vaccine in patients who underwent transplantation

VZV IgG levels and the number of VZV SFCs in patients who underwent lung transplantation were evaluated. Data after vaccination were selected at the following time points: closest before transplantation (Tv), around 1 month after transplantation (Tx0), and around 6 months or longer after transplantation (Tx1). In vaccinated patients, VZV IgG levels were highest at Tv (GMFR over T0 = 2.07, $p < 0.001$), and then they continuously decreased after transplantation. In unvaccinated patients, however, VZV IgG levels were lowest at Tx0 (Figure 5a). Regarding CMI, the number of VZV SFCs was higher in vaccinated patients at different corresponding time points than in unvaccinated patients, especially at T0 ($p = 0.047$). No significant change in the number of VZV SFCs was found between T0 and Tv. At Tx0, VZV SFC levels significantly decreased in vaccinated patients compared with both at T0 ($p = 0.003$) and Tv ($p < 0.001$), likewise in unvaccinated patients compared with T0. However, in both vaccinated and unvaccinated patients, VZV SFC levels increased again to relatively high levels at Tx1 (46.2 ± 46.9 and 25.6 ± 27.1, respectively), meaning a 51% and 33% increase compared with the levels at Tx0 (Figure 5b).

Safety of HZ vaccine

A total of 2 unvaccinated patients had a single dermatome HZ during the study period (at 10 and 18 months after transplantation, respectively). A total of 1 vaccinated patient had a single dermatome HZ at 9 months after transplantation, which was already 3 years after receiving HZ vaccination. Swelling and red rash at injection sites were documented in 2 vaccinated subjects. There were no signs of new development or booster of allogeneic antibodies hampering the transplantation or worse, and early transplant outcome was unaffected by the vaccination.

Discussion

In this paper, we show that Zostavax use is safe in patients with ESPD awaiting lung transplantation. Vaccine efficacy was shown with a good humoral immune response. Cellular immunity was also higher in vaccinated patients before transplantation. Both the gender and type of ESPD of patients did not affect the immune response to the vaccine. After transplantation, there is a clear decrease in VZV-specific IFN-γ–producing T cells, most probably due to the intense immune suppression. Recovery of cellular immunity occurred in both vaccinated and unvaccinated patients. There was no clear protection from HZ detectable because of the limited number of patients involved and the low incidence of HZ in both groups.

We observed the peak of VZV IgG response within 3 months after vaccination in the patient group, followed by a gradual decline, but the levels were still higher at 12 months after vaccination than at baseline (1.76 GMFR to T0), which is consistent with the immunogenicity of HZ vaccine in healthy subjects.[20–22] It is notable that a stronger humoral response to Zostavax was seen in younger patients. A total of 16 patients were younger than 50 years when receiving the vaccination. VZV IgG titers in 2 patients (aged 19 and 26 years) were increased almost 10 times at the first time point after vaccination (<3 months) compared with the titers at baseline. Although Zostavax is licensed for persons aged ≥50 years and recommended for routine vaccination of people aged ≥60 years,[17] considering the high risk of HZ, patients under the age of 50 years awaiting transplantation may also benefit from immunization with HZ vaccine.

Although boosted VZV IgG titers at 6 weeks after HZ vaccination have been shown to be strongly inversely

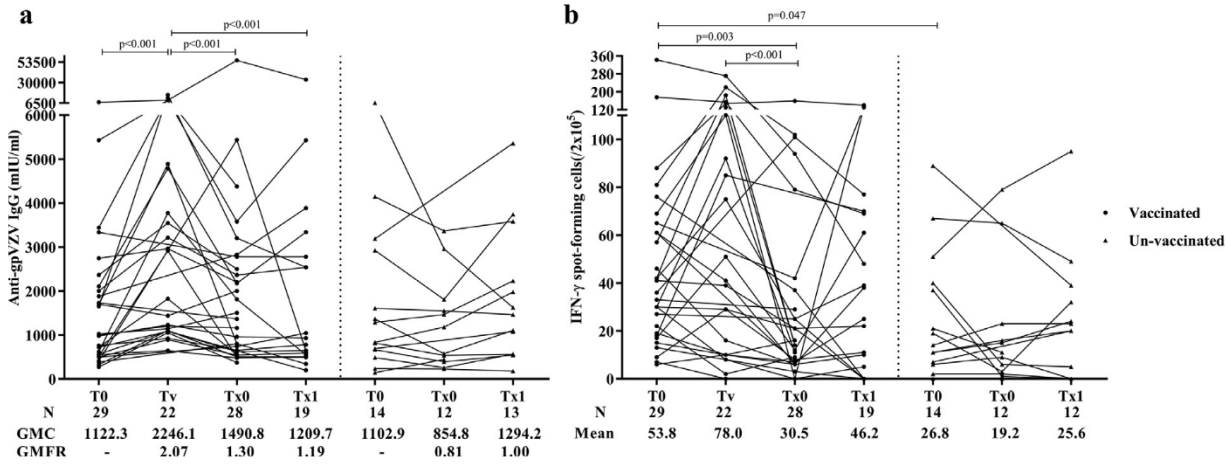

Figure 5 Humoral and cellular immune response in transplant patients. (a) Levels of anti-gpVZV antibody in vaccinated and unvaccinated patients before and after transplantation.. (b) Number of IFN-γ–secreting T-cells spots in response to VZV stimulation in vaccinated and unvaccinated patients before and after transplantation. GMFR at different time points after vaccination over T0 and mean of the number of IFN-γ–secreting T-cells spots are shown under each figure. GMC, geometric mean concentration; GMFR, geometric mean fold rise; gp, glycoprotein; IFN, interferon; IgG, immunoglobulin G; N, number of subjects at different time point; T0, baseline; Tv, closest before transplantation; Tx0, 1 month after transplantation; Tx1, 6 months or longer after transplantation; VZV, varicella–zoster virus.

correlated with the risk for HZ, fold rise in VZV IgG antibody titers was not considered a mechanistic correlate of protection for HZ. In contrast to the humoral response, VZV-specific CMI is considered to be more important to prevent VZV reactivation.[23,24] In this study, we performed an IFN-γ ELISpot assay to evaluate VZV-specific CMI. Compared with intracellular flow cytometric analysis, ELISpot assay is suggested to be a more sensitive method to evaluate low-level CMI responses and to better reflect the effector function of T cells during VZV stimulation.[25] Similar to the VZV IgG levels, the number of VZV SFCs was highest within 3 months after vaccination, and younger patients showed higher VZV SFCs levels.

When vaccinated patients were stratified according to age, CMV status, and VZV IgG/VZV SFCs levels at baseline, we found that patients with high baseline immunity to VZV can maintain relatively high levels of both VZV IgG and VZV SFCs levels after HZ vaccination. CMV seropositivity showed a positive effect on VZV IgG response but a negative effect on VZV CMI response to the HZ vaccine. These findings were confirmed by the multilevel analysis, which showed that CMV status, ln VZV IgG levels, and ln VZV SFCs levels at baseline significantly predicted subsequent immune responses. A previous HZ vaccine efficiency study in healthy people also found that vaccinated persons with higher VZV CMI baseline levels had higher levels of VZV CMI after vaccination.[26] The authors suggested that individuals with lower baseline levels of VZV CMI could have limited VZV-specific memory T cells or more regulatory cells leading to lower ability to respond to HZ vaccination. As for CMV, there are some studies evaluating the CMV status on influenza vaccine, but no consistent conclusions were made about the effect of latent CMV infection on antibody response.[27] Chronic CMV infection has been shown to drive immunosenescence and influence the T-cell compartment,[28] and this could indirectly affect the vaccine responses. Interestingly, age was shown to be significantly associated with VZV IgG but not VZV SFCs levels in the multilevel analysis. In other studies, age was correlated with VZV CMI levels.[20,26] This could be due to the limitation of our VZV CMI data. VZV CMI response to HZ vaccine was demonstrated to increase to a high level shortly after vaccination, with the peak level detected at 1 to 6 weeks[20,21,26] after vaccination and then declined significantly for 1 year after vaccination. In our study, the majority of the samples for ELISpot assays were done more than 6 weeks after vaccination, so VZV SFCs levels might be lower early after vaccination.

The interval between T0 and Tx0 in vaccinated patients who underwent transplantation varied between 2.1 months and 27.4 months. VZV IgG and VZV SFCs levels after transplantation were impacted by the combination of vaccination, immunosuppressant, and treatments for rejection/infections. With the small numbers of patients after transplantation, this study is not powered enough to conduct multilevel analysis. In vaccinated patients who underwent lung transplantation, VZV IgG concentrations declined starting at 1 month after transplantation, but they were still higher than at baseline levels during the follow-up period, in contrast to the relatively stable level in unvaccinated patients who underwent transplantation.[29] Lowest VZV SFCs levels were seen at 1 month after transplantation in both groups, and this could be due to the strong effects of short-term immunosuppressants, which target T lymphocytes. VZV-specific CMI returned to a high level after a median time of 7.3 months after transplantation. This T-cell immunity recovery was expected because a lower dose of immunosuppressive treatments was given at Tx1 than at Tx0. Of note, VZV SFCs levels in vaccinated patients were significantly higher at baseline than those in unvaccinated patients. This can be influenced by the fact that unvaccinated patients were significantly older at baseline than vaccinated patients ($p = 0.040$).

As for the safety of HZ vaccine, no serious adverse events were found related to the HZ vaccine. Although 5 patients received the HZ vaccine around 1 month before transplantation, no vaccine-related HZ was reported after vaccination. The only vaccinated patient who had HZ experienced this at 3 years after vaccination. We did not see the impact of the HZ vaccine on graft outcomes, and no correlation was found between vaccination response and antiviral prophylaxis, rejection, or infection.

This study has several limitations. First, the number of transplant patients limited the power of testing for the efficiency of the HZ vaccine after transplantation. Second, although ELISpot assay shows the frequency of IFN-γ–secreting cells in response to VZV stimulation in PBMCs, most of these cells are CD4+ T cells. CD8+ T cells and cells producing other cytokines were not investigated. In addition, the incidence of HZ could also be influenced by immunosuppressant, anti-CMV/-herpes prophylaxis, and treatment for rejection after transplantation.[30–32] Almost all atients who underwent transplantation were treated with standard immunosuppressive regimens, so we could not assess the influence of these medications on HZ vaccination. In addition, the follow-up duration of our study was around 1 year; thus, the long-term effect of vaccination on the incidence of HZ after transplantation could not be evaluated yet. Longer observations and study of possible different vaccines in transplant patients are needed.

In conclusion, we found that the live-attenuated HZ vaccine was safe and induced robust humoral and cellular response in patients with ESPD before lung transplantation. Vaccinated patients showed good recovery of VZV CMI levels after transplantation. Of note, patients younger than the recommended vaccination age could also benefit from pre-transplant immunization. Recently, a 2-dose recombinant sub-unit vaccine (Shingrix, GlaxoSmithKline) has become available in some countries, with a higher efficacy for preventing HZ and PHN than Zostavax. The efficacy of the sub-unit vaccine did not decline with age and was safer for immunocompromised patients because of the absence of live virus.[33] Studies about safety and immunogenicity of Shingrix in patients requiring lung transplantation are needed in the future.

Disclosure statement

The authors have no conflicts of interest to disclose.

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