Safety and immunogenicity of adjuvanted recombinant subunit herpes zoster vaccine in lung transplant recipients

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Abstract

Lung transplant recipients are at high risk for herpes zoster and preventive measures are a significant unmet need. We investigated the safety and immunogenicity of two doses of a recombinant zoster vaccine (RZV) in lung transplant recipients (50 years). We enrolled 50 patients of which 49 received at least one vaccine dose. Anti-glycoprotein E (gE) antibody levels (n = 43) increased significantly compared to baseline (median optical density [OD] 1.96; interquartile range [IQR]: 1.17–2.89) after the first (median OD 3.41, IQR 2.54–3.81, $p < .0001$) and second vaccine dose (median OD 3.63, IQR 3.39–3.86, $p < .0001$). gE-specific polyfunctional CD4+ T cell frequencies (n = 38) also increased from baseline (median 85 per 10^6 CD4+ T cells; IQR: 46–180) to the first (median 128 per 10^6 CD4+ T cells; IQR: 82–353; $p = .023$) and after the second dose (median 361 per 10^6 CD4+ T cells; IQR: 146–848; $p < .0001$). Tenderness (83.0%; 95%CI: 69.2–92.4%) and redness (31.9%; 95%CI: 19.1–47.1%) at injection site were common. One rejection episode within 3 weeks of vaccination was observed. This is the first study demonstrating that RZV was safe and elicited significant humoral and cell-mediated immunity in lung transplant recipients. RZV is a new option for the prevention of shingles in this population.

1 | INTRODUCTION

Varicella zoster virus (VZV) infects humans early in life and thereafter establishes lifelong latency in sensory nerve ganglia.[1] Herpes zoster (HZ) results from reactivation of latent VZV, often causing painful dermatomal eruption or disseminated disease. Complications of VZV occur in 15–40% of cases, the most common being postherpetic neuralgia.[2–4] Individuals with diminished cellular immunity to VZV are at increased risk for HZ and the rate of complications is significantly higher in this population.[5,6] Notably, solid organ transplant (SOT) recipients have a predominant cellular immune deficit, caused by chronic immunosuppressive treatment after transplantation. As such, the HZ incidence rate is significantly higher in SOT recipients compared to the general population.[7,8] However, the HZ risk varies depending on the type of transplanted organ: lung transplant recipients in particular are more likely to reactivate VZV compared to abdominal organ transplant recipients.[7,8] Epidemiologic studies report a cumulative HZ incidence in lung transplant recipients of 15–20% within the first 5 years after transplantation.[7,9] Recurrent HZ is common (13.8%) in lung transplant recipients and a high proportion of patients (20%) develop postherpetic neuralgia.[9]

The adjuvanted recombinant zoster vaccine (RZV; Shingrix™, GSK) is a two-dose nonlive vaccine that contains 50 μg of the external domain of the VZV glycoprotein E (gE) in combination with the AS01B Adjuvant System. RZV is efficacious in preventing HZ in adults 50 years of age and is licensed in North America and Europe for this indication.[10,11] A recent study also showed that RZV was immunogenic and safe in kidney transplant recipients aged 18 years, under chronic immunosuppressive therapy.[12]

There is an urgent need for HZ preventive strategies in high-risk patients such as lung transplant recipients. However, due to the intense immunosuppressive therapy required to avoid allograft rejection in this population compared to other types of organ transplants, the ability to mount an immune response to vaccines may be limited. We therefore assessed the immunogenicity and safety of RZV in lung transplant recipients in this study.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This single arm RZV immunogenicity study was conducted as part of a tertiary care lung transplant program at the University Health Network Transplant Centre, Toronto. Consecutive single or double lung transplant recipients who were 50 years of age were approached in outpatient transplant clinic from March 2018 to August 2018. Patients were eligible if they were 90 days posttransplant and had positive varicella zoster IgG antibodies before transplantation (see details in Supporting Information). The study was registered at ClinicalTrials.gov (NCT03493776).

After obtaining written informed consent, lung transplant recipients received two intramuscular doses of RZV (0.5 mL) 2–6 months apart. Serum and whole blood were obtained immediately before the first vaccination (baseline), immediately before the second vaccination (T1), and 3–6 weeks after the second vaccination (T2). The primary outcomes of the study were cellular and humoral immune responses to RZV vaccination. The secondary outcome was the safety of the vaccine.

2.2 | Assessment of immunogenicity

The humoral immune response was evaluated using an enzyme-linked immunosorbent assay (ELISA) targeting VZV glycoprotein E (gE) antibodies at T1 and T2 as compared to baseline.[13] Testing was performed at the VZV reference laboratory at the Centers for Disease Control and Prevention (CDC). Results were expressed as optical density (OD) values. Avidity testing of anti-gE antibodies was also performed.

In order to assess the cell-mediated immune response, we modified previously described methods.[14,15] The frequencies of gE-specific CD4^{2+} T cells (CD4+T cells expressing two or more activation markers of the four assessed: interferon-γ, interleukin-2, tumor necrosis factor–α, and CD40 ligand) were measured, after in vitro stimulation with a pool of one hundred and fifty-three 15-mer peptides (1.25 μg/mL each, overlapping by 11 amino acids) which span the entire VZV gE protein (JPT Peptide Technologies, Berlin, Germany), by intracellular cytokine staining and detection by flow cytometry as previously established by others.[12,16–22] Details are provided in the Supporting Information.

2.3 | Assessment of reactogenicity and safety

Standardized diaries were provided to all participants to record solicited local and general adverse events for 7 days after each vaccination (see details in Supporting Information). All solicited local and generalized symptoms were considered causally related to the vaccine. Unsolicited adverse events such as hospitalizations and rejection episodes were collected until 3 months after the last vaccine dose. For patients who had only one vaccine dose, unsolicited adverse events were collected until the latest possible time point for administration of the second dose (6 months after the first vaccine). Allograft rejection was defined as biopsy proven or clinically suspected and treated. We also performed a 2-year follow-up by chart review of these patients for the occurrence of shingles.

2.4 | Statistical analysis

The sample size of 50 patients was based on feasibility and enrollment of at least 10% of the prevalent lung transplant population over age 50 years during the study period. Reactogenicity and safety results were analyzed in all participants who were vaccinated with at least one dose of RZV. The analyses of humoral and cellular immune responses were performed in patients for whom all baseline and postvaccine specimens were available (provided the PBMC counts allowed the assay to be performed) (Figure 1). For group comparisons, chi-squared or Fisher exact test was used for dichotomous variables, whereas Mann–Whitney U test was used for continuous variables. We used Wilcoxon signed rank test for paired analysis. Values of $p < .05$ were considered statistically significant. Statistics were done in GraphPad version 7.0 and in STATA version 16.0 (Stata Corp.). Graphs

were made using GraphPad version 7.0 or National Institute of Health (NIH)'s Simplified presentation of incredibly complex evaluations (SPICE).[23]

3 | RESULTS

3.1 | Study participants

We enrolled a total of 50 lung transplant recipients. Of these, 49 patients received at least one vaccine dose (Figure 1). The median age of participants was 65.4 years (IQR: 59.1–70.6). Most participants were men (29/49; 59.2%) and most had a double vs. single lung transplant (40/49; 80.1%) (Table 1). The median time from transplant to the first vaccination was 3.0 years (IQR: 1.0–5.0). The median interval between the first and second vaccine was 63 days (IQR: 62–69). Except for one patient, all participants were on triple immunosuppressive treatment with median trough levels for cyclosporine (192 ng/mL; IQR: 155–227) or tacrolimus (12.5 ng/mL; IQR: 7.2–14.9) at time of the first vaccine.

3.2 | Humoral immune response

Serum samples at all time points were available for 43 lung transplant recipients (Figure 1). The VZV gE antibody concentration increased significantly compared to baseline (median OD 1.96; IQR: 1.17–2.89) after the first (median OD 3.41, IQR 2.54–3.81, p < .0001) and the second vaccine dose (median OD 3.63, IQR 3.39–3.86, p < .0001; Figure 2A). At baseline, gE-specific antibody avidity was relatively low (46.4%, IQR: 36.6–63.4). Noteworthy, the avidity of the antibodies increased significantly after the first (71.5%; IQR: 52.9–91.5; p < .0001) and the second vaccine (84.2%; IQR: 59.4–96.5; p < .0001) (Figure 2B). There was a strong positive correlation between VZV anti-gE antibody concentrations (as by OD) and the avidity of anti-gE antibodies at baseline (Spearman's rho = 0.6442; p < .0001) after the first (Spearman's rho = 0.8325; p < .0001) and after the second vaccine (Spearman's rho = 0.7338; p < .0001). Further analysis did not show a significant correlation between anti-gE antibody concentrations and patient age or time from transplant to vaccination (data not shown) but showed an inverse correlation between dose of mycophenolate and antibody concentration (Spearman's rho = −0.3447; p = .019).

3.3 | Cell-mediated immune response

Cell-mediated immune responses were analyzed for 38 patients (Figure 1). VZV gE-specific $CD4^{2+}$ T cell frequencies increased significantly from baseline (median 85 $CD4^{2+}$ T cells per 10^6 CD4T cells; IQR: 46–180) to after the first vaccine (median 128 $CD4^{2+}$ T cells per 10^6 CD4T cells; IQR 82–353; p = .023) and after the second vaccine (median 361 $CD4^{2+}$ T cells per 10^6 CD4T cells; IQR: 146–848; p < .0001) (Figure 3). Among VZV gE-specific $CD4^{2+}$ T cells, IL-2+CD40L+ CD4 T cells contributed the most to the polyfunctional signature (Figure 4). There was no significant increase in VZV-specific CD8 T cells due to vaccination (data not shown). Patients with a longer interval between transplantation and vaccination had higher frequencies of $CD4^{2+}$ T cells at baseline (Spearman's rho = 0.4118; p = .0102) and a trend toward higher gE-specific $CD4^{2+}$ T cells after the second vaccine dose (Spearman's rho = 0.3184; p = .0514). There was no correlation with age and the frequencies of $CD4^{2+}$ T cells at baseline or after vaccination (data not shown).

Anti-gE antibody concentrations (as by OD) and the number of gE-specific CD4^{2+} T cells were not correlated at any of the different time points (data not shown).

3.4 | Reactogenicity and safety

Forty-nine participants received at least one vaccine dose (included in the safety analysis for unsolicited adverse events). Of these, 47 of 49 completed the standardized diary for capturing solicited adverse events after the first vaccine dose and 44 of 45 completed the diary after the second vaccine dose.

During the 7-day postvaccination follow-up for solicited adverse events, the most common local adverse event was tenderness at injection site reported by 83.0% (95% CI: 69.2–92.4%) (39/47), followed by redness (31.9%; 95% CI: 19.1–47.1%) (15/47) and swelling (26.7%; 95% CI: 14.6–41.9%) (12/45). Only a minority of these events were classified as grade 3; all were self-limited (Figure 5). When occurring, local adverse events were of short duration. Tenderness at injection time resolved after a median of 2 days (IQR: 2–3 days), so did redness (IQR: 1–3 days) and swelling (IQR: 2–3 days). The most frequent generalized solicited symptoms were myalgia (36.2%; 95% CI 22.7–51.5; 17/47), fatigue (31.9%; 95% CI 19.1–47.1; 15/47), and headache (23.4%; 95% CI 12.3–38.0; 11/47). Gastrointestinal complaints (6.4%; 95% CI 1.3–17.5; 3/47) and shivering (4.3%; 95% CI 0.5–14.5; 2/47) were rare, and no participant developed fever within 7 days after injection.

From the first vaccination to months 3 after the last immunization, we recorded 26 unsolicited adverse events of which 14 were severe adverse events (Table E1 Supporting Information). Throughout the study, one death was reported (respiratory failure due to laboratory-confirmed influenza B infection) which we considered unrelated to vaccination. Two patients developed a HZ infection during the study 2-year follow-up for occurrence of shingles (with no cases occurring after the second vaccine dose): one participant experienced a mono-dermatomal infection 2 days after the first vaccine dose. The patient had treatment with valacyclovir and recovered without sequelae. In retrospect, this patient already had symptoms of reactivation (pain at reactivation site) at the time of vaccination. The second participant developed a disseminated herpes zoster episode 32 days after the first vaccine dose. This patient's lesions resolved with intravenous acyclovir although he developed postherpetic neuralgia.

Three participants, all of whom were within the first year posttransplant, experienced four rejection episodes (none documented to be antibody-mediated). One lung transplant recipient had two episodes of clinically suspected rejection 89 and 130 days after the first vaccination (both episodes before the second vaccine dose), respectively. Due to the long interval between suspected rejection and RZV immunization, these rejection episodes were classified as unrelated to vaccination. Two participants experienced a histologically proven cellular rejection episode (both grade A1 according to the ISHLT classification[24]) at 17 days and 90 days after second vaccination, respectively.

Protocol biopsies and DSA measurements for clinical purposes in our program were done at 1, 3, 6, 9, 12, 18, 24 months posttransplant and repeated if rejection was suspected. Based on this, there were 11 patients in the study cohort (all recently transplanted within the first

2 years) who had DSA measured in the 3 months prior to first vaccine and up to 3 months after the second dose of vaccine. Of these, only one patient developed new weak positive DSA compared to prevaccination. The patient was 9 months posttransplant and a biopsy done at that time showed no rejection.

4 | DISCUSSION

We conducted a study to assess the immunogenicity and safety of recombinant zoster vaccine in lung transplant recipients 50 years of age. The major findings of our study were as follows: (a) We found that RZV vaccination elicits a significant increase in VZV gE-specific antibody; (b) the vaccine also enhances the strength (avidity) with which IgG antibodies bind to VZV gE; (c) RZV induces a significant cell-mediated immune response as determined by the number of VZV gE-specific polyfunctional CD4 T cells; (d) adverse events at the injection site were common but of short duration and of mild severity; and (e) there were no severe rejection episodes with temporal association to the vaccine; and (f) no clinical cases of zoster were observed after the second vaccine dose during a 2-year follow-up period.

To our knowledge, this represents the first study that systematically examines serologic and cellular immune responses to RZV in lung transplant recipients, the most vulnerable group to HZ among SOT recipients.[7] Our findings are consistent with previously reported studies showing that RZV elicits anti-gE humoral and cellular immune responses in nonimmunocompromised individuals 50 years of age.[19–21,25,26]

The only study published so far that examined RZV-associated immune responses in organ transplant recipients was restricted to kidney transplant patients.[12] The humoral vaccine response rate (defined as 4-fold increase in antibody titer) was 80.2% and no apparent difference in anti-gE antibody geometric mean antibody concentration was seen linked to the types of maintenance immunosuppressive therapy. Humoral immune responses appeared lower for participants 50 years of age compared to younger kidney transplant recipients. Median gE-specific $CD4^{2+}$ frequencies prevaccination were low (21 cells/10^6 CD4 T cells) and increased significantly 4 weeks after the second vaccine dose (2149 cells/10^6 CD4 T cells). Consistent with the findings in kidney transplant recipients, we also found a significant antibody response in lung transplant recipients after RZV immunization. Since our antibody assay was a CDC performed assay using optical density vs. the in-house GSK assay used in other studies, an exact comparison of antibody concentrations between studies is not possible. However, this is of less relevance because the antibody cutoffs for HZ prevention are not known. Nonetheless, we do demonstrate that there is a statistically significant increase in antibody levels after vaccination in lung transplant recipients ($p <$ .001). A unique aspect of our assessment was the measurement of antibody avidity which provides further evidence of a robust antibody response. In accordance with the previously reported results for nonimmunocompromised individuals[19–21,26] and for kidney transplant patients,[12] we also found a significant increase in polyfunctional gE-specific T cells.

In the immunocompetent population, IL-2+ CD40L+ double-positive cells account for the majority of vaccine induced gE-specific $CD4^{2+}$ T cells.[20,21] Consistent with the findings

in immunocompetent individuals, the largest gE-specific $CD4^{2+}$ cell population after RZV immunization of lung transplant recipients were also IL-2+CD40L+ double-positive cells. Therefore, the immunosuppressive treatment associated with lung transplantation does not obviously affect the signature of polyfunctional gE-specific CD4 T cells.

There was a weak to moderate, statistically significant, inverse correlation (Spearman's rho = −0.3447; p = .019) of mycophenolate dose and vaccine-elicited antibody concentration. An inverse correlation of mycophenolate dose and vaccine-elicited antibody response is an observed phenomenon that has previously been noted in studies of influenza vaccines in the transplant setting.[27] However, preemptive reduction in mycophenolate doses has not been studied and is generally not advised to overcome the reduced immune response.

Reactions at the injection site such as tenderness (83.0%), redness (31.9%), and swelling (26.7%) were common after immunization. The frequency of these reactions among lung transplant patients is similar compared to kidney transplant recipients[12] and nonimmunocompromised individuals.[10,11,19,21] We recorded two biopsy-proven rejection episodes and two clinically suspected and treated rejection episodes after RZV vaccination. All rejection episodes were mild and three out of four rejection episodes occurred more than 30 days after the last vaccine dose and were therefore considered unrelated to RZV vaccination. All episodes were in patients who were within the first posttransplant year. According to ISHLT registry data, 26.6% of lung transplant recipients will require treatment for acute rejection in the first year posttransplant.[28] The frequency of biopsy-proven allograft rejections in kidney transplant recipients was similar in the placebo group (3.0%) compared to RZV vaccination (5.3%) in apreviousstudy.[12] In our study, two patients developed HZ after the first vaccine. The first patient already had symptoms at enrollment and the second patient developed the infection >30 days after the first dose of vaccine. We therefore did not consider these events related to the vaccine.

One strength of our study includes its unique population of highly immune suppressed lung transplant recipients and an in-depth analysis of the vaccine-elicited immune response, including quantitative and qualitative antibody responses and cell-mediated immune response. By choosing the polyfunctional CD4+ T cell response as a primary endpoint for cell-mediated immunity, we ensured that we are assessing CD4 responses of high quality, capable of eliciting potent and durable T cell responses.[29] This approach has previously been chosen by others to characterize gE-specific CMI[12,16–22] and it has been shown that CD4+ T cells which express at least two activation markers are more long-lasting compared to single positive cells.[20] A limitation of our study is the absence of a control group although a placebo control would not be ethical since in Canada, vaccine is recommended for everyone over age 50 years. This means that the rate of adverse events after vaccination may be overestimated in our study, as it cannot be compared to adverse events after placebo injection. In addition, the lack of a healthy population comparator means that we are unable to compare relative immunogenicity. However, there are also no serological or CMI correlates of protection established for vaccine efficacy. In addition, since standardized measurements of gE-specific CMI and gE-specific antibodies are not available, the counts of gE-specific polyfunctional CD4+ T cells and the concentrations of antibodies cannot be directly compared with previous studies using different assays.

Although our study population was small, it was sufficient to provide immunologic and safety data and represented 10% of our total prevalent lung transplant cohort 50 years of age. The study did not examine the long-term durability of immune responses or memory B cell formation. These aspects could be a focus for future studies.

In summary, we provide novel information on the immune response elicited by RZV vaccination in lung transplant recipients. We show that the vaccine induces cell-mediated and humoral immune responses in this severely immunocompromised population at high risk for herpes zoster. Our study suggests that RZV can be used to prevent shingles in the lung transplant population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Abbreviations:

AI	avidity index
CD40L	CD40 ligand
CDC	Centers for Disease Control and Prevention
CMI	cell-mediated immunity
CMV	cytomegalovirus
DEA	diethylamine
ELISA	enzyme-linked immunosorbent assay
gE	glycoprotein E
GSK	GlaxoSmithKline
HIV	human immunodeficiency virus
HZ	Herpes zoster
IFN-γ	interferon-γ

IgG	Immunoglobulin G
IL-2	interleukin-2
IQR	interquartile range
ISHLT	International Society for Heart and Lung Transplantation
IVIG	intravenous immunoglobulins
OD	optical density
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
RZV	recombinant herpes zoster vaccine
SFC	spot forming cell
SOT	solid organ transplant
SPICE	simplified presentation of incredibly complex evaluations
TNF-α	tumor necrosis factor-α
US	United States
VZV	varicella zoster virus.

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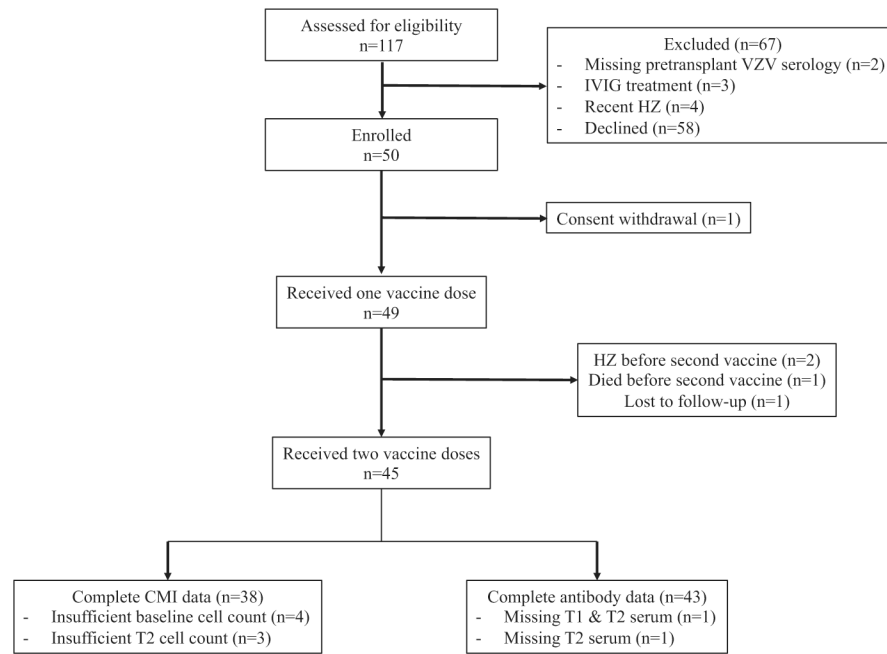
FIGURE 1.

Participant flowchart. CMI, cell-mediated immunity; HZ, Herpes zoster; IVIG, intravenous immunoglobulin; T1, postdose 1 visit; T2, postdose 2 visit; VZV, varicella zoster virus
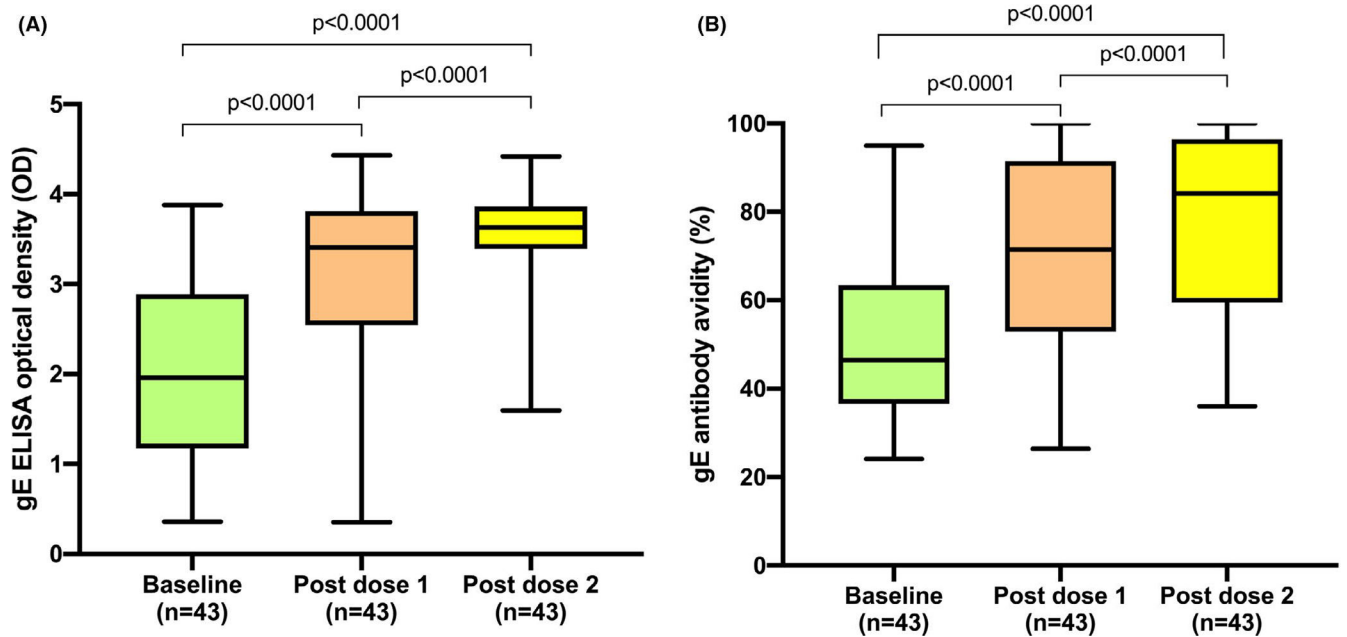
FIGURE 2.
Antibody response to recombinant herpes zoster subunit vaccine. A, Anti-glycoprotein E antibody concentration expressed as optical density. Whiskers represent maximal and minimal values. Boxes delimit upper and lower quartiles. B, Anti-glycoprotein E antibody avidity. Whiskers represent maximal and minimal values. Boxes delineate upper and lower quartiles. ELISA, enzyme-linked immunosorbent assay; gE, glycoprotein E; OD, optical density
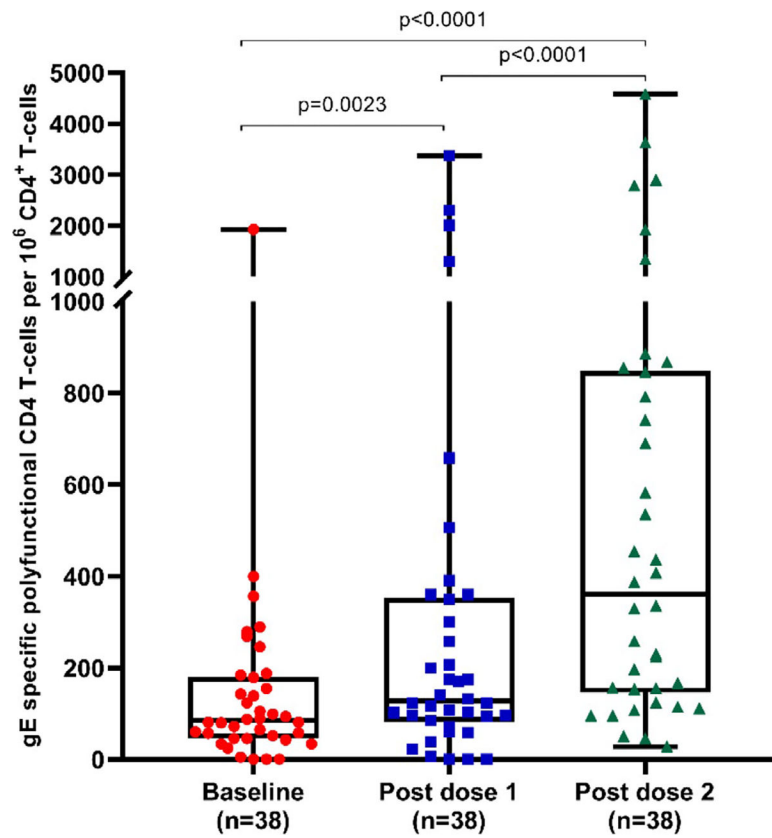
FIGURE 3.
Cell-mediated immune response to recombinant herpes zoster subunit vaccine. Glycoprotein E specific $CD4^{2+}$ frequencies (polyfunctional CD4+ T cells) per 10^6 $CD4^+$ T cells. Whiskers represent maximal and minimal values. Boxes delineate upper and lower quartiles. gE, glycoprotein E
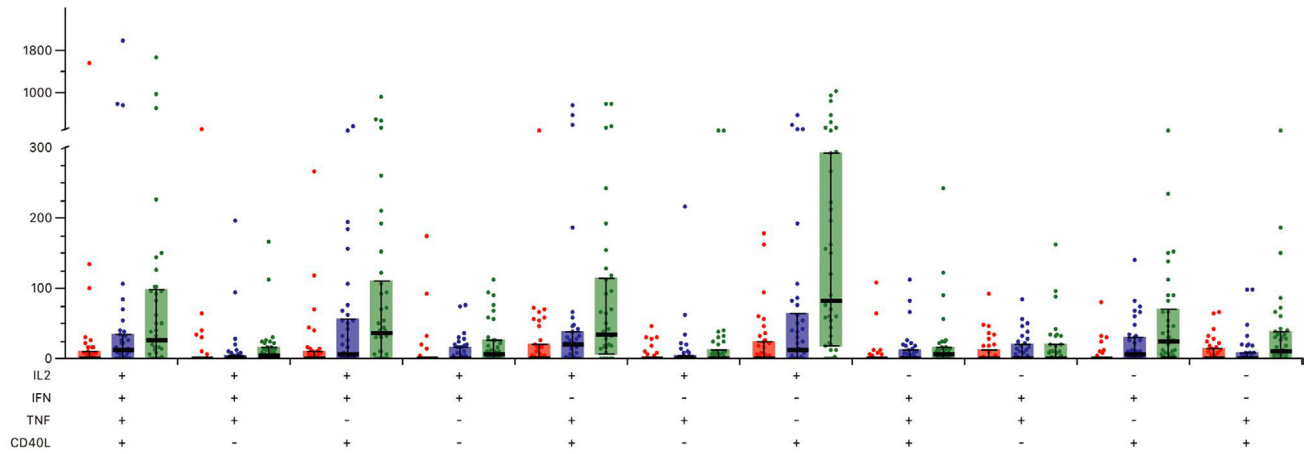
FIGURE 4.
Frequency of gE-specific CD4T cells expressing at least two activation markers. Bold
bar indicates median number of cells. Whiskers indicate upper and lower interquartile
range. Abbreviations: CD40L, CD40 ligand; gE, glycoprotein E; IL-2, interleukin-2; IFN-γ,
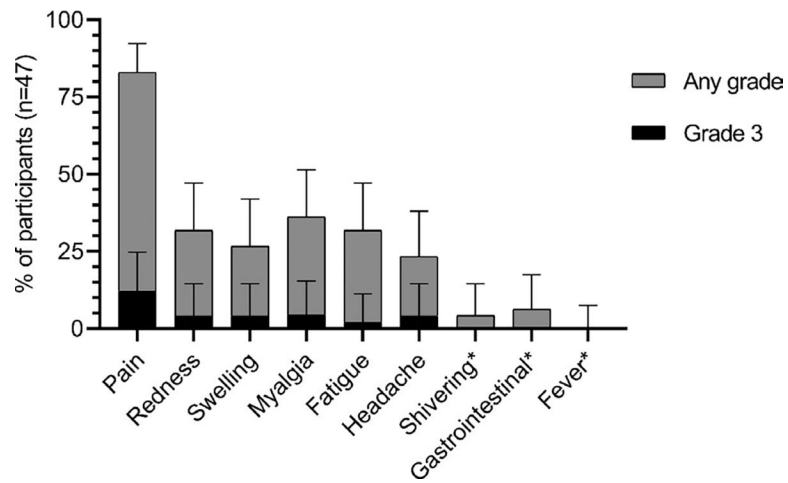interferon gamma; TNF-α, tumor necrosis factor alpha

FIGURE 5.
Solicited adverse events. Error bars indicate 95% confidence intervals. Fever was defined as a body temperature 38.0°C. *No grading of symptom severity for shivering, gastrointestinal symptoms (nausea / vomiting), and fever. N, number of participants with at least one vaccine dose administered and completed adverse events diary. Events occurred either after the first dose or second dose

TABLE 1

Characteristics of lung transplant recipients who received at least one dose of recombinant zoster vaccine

Characteristics	N = 49
Age (years) [median (IQR)]	65.4 (59.1–70.6)
Male (%)	29 (59.2)
Time from transplant to first vaccine (years) [median (IQR)]	3.0 (1.0–5.0)
Within first year of transplantation (%)	12 (24.5)
Double lung transplant (%)	40 (81.6)
Previous live attenuated herpes zoster vaccine[a] (%)	12 (24.5)
Previous herpes zoster episode[a] (%)	7 (14.3)
Underlying lung disease (%)	
Idiopathic pulmonary fibrosis	21 (42.6)
COPD	11 (22.4)
Cystic Fibrosis	2 (4.1)
Other	15 (30.6)
Antithymocyte globulin 3–6 months prior (%)	2 (4.1)
Basiliximab 3–6 months prior (%)	3 (6.1)
Immunosuppression	
Prednisone (%)	49 (100.0)
Prednisone dose (mg/day) [median (IQR)]	10 (5–10)
Tacrolimus (%)	16 (33.3)
Tacrolimus trough level (ng/ml) [median (IQR)]	12.5 (7.2–14.9)
Cyclosporin (%)	33 (66.6)
Cyclosporin trough level (ng/ml) [median (IQR)]	192 (155–227)
Mycophenolate mofetil / Mycophenolate sodium (%)	41 (83.7)
Azathioprine (%)	7 (14.3)

Data apply to all patients who received at least one dose of herpes zoster subunit vaccine.

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a]Based on self-report at time of enrollment.