Herpes zoster after lung transplantation boosts varicella zoster virus–specific adaptive immune responses

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KEYWORDS: VZV; ELISpot; IFN-γ; memory cells; B cells

BACKGROUND: Varicella zoster virus (VZV)-specific memory T cells are significantly lower in transplant recipients than in controls. In addition, VZV-specific immunoglobulin G titers are significantly lower after than before transplantation. Data on the incidence and timing of herpes zoster (HZ) after lung transplantation are limited. This study had two aims: first, we investigated the incidence and severity of HZ after lung transplantation; second, we determined the systemic VZV-specific T-cell and B-cell memory responses before and after HZ.

METHODS: The records of 119 patients who underwent transplantation were analyzed for post-transplant HZ. The VZV-specific B-cell and T-cell memory responses of 5 patients before and after HZ were compared with 5 patients without HZ by enzyme-linked immunospot assay and flow cytometry, respectively.

RESULTS: HZ was clinically diagnosed and confirmed by polymerase chain reaction on blister fluids and/or plasma in 17 transplant recipients. Uncomplicated cutaneous HZ was present in 12 patients, and 5 patients had disseminated HZ, of whom 1 died. The incidence of HZ after transplantation (38.2 cases/1,000 patient-years) was significantly higher than the age-matched healthy population (7–8 cases/1,000 patient-years). The frequency of VZV-specific immunoglobulin G–producing B cells (p = 0.06) and the percentage of VZV-specific CD4 and CD8 memory T cells increased after HZ to higher frequencies than in patients without HZ (p = 0.03). This was mainly attributed to VZV-reactive effector memory CD4 T cells (p = 0.02) and central memory (p = 0.02) and effector memory (p = 0.03) CD8 T cells.

CONCLUSIONS: Lung transplant recipients are highly prone to develop HZ with severe complications. Despite deep immunosuppression, HZ boosted their systemic VZV-specific B-cell and T-cell memory responses.

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The varicella zoster virus (VZV) belongs to the alpha sub-family of the human herpesvirus family. Primary VZV infection principally occurs during early childhood and presents as varicella. Thereafter, VZV establishes a life-long
latent infection in sensory ganglia along the entire neuraxis. VZV may reactivate later in life when virus-specific T-cell immunity wanes because of old age or immune suppression, resulting in herpes zoster (HZ). HZ may be accompanied with complications such as zoster ophthalmicus, bacterial superinfections, pneumonitis, and neurologic complications, including post-herpetic neuralgia (PHN), meningitis, and encephalitis.1–3

In the Netherlands, with a VZV seroprevalence of >95% at 6 years old, no national pediatric VZV immunization program is installed.4 The incidence of HZ has an inflection point at 50 years of age and ranges from an incidence of 1 to 4 cases per 1,000 patient-years (PY) at 40 to 50 years to 10 cases per 1,000 PY at 80 years.3–5 Annual reported rates of hospitalization for HZ vary extensively, from 2.1 to 16.1 per 100,000 population.6,7 VZV infections in transplant recipients can be extremely serious, with multiorgan failure and eventually death. Solid-organ transplant recipients are at increased risk of HZ, and the incidence of severe VZV-induced illness ranges from 7.4% to 45% after transplantation.8–12

Primary VZV infection induces the generation of a specific T-cell and B-cell responses. Systemic memory VZV-specific T cells are maintained at a low frequency. VZV-specific T cells, both CD4 and CD8 T cells, are pivotal to controlling the primary infection and preventing viral reactivation.13,14 We recently reported that monocyte-derived dendritic cells (moDCs) infected with VZV are efficient antigen-presenting cells (APCs) applicable to enumerate and characterize the phenotype and differentiation status of the systemic VZV-specific CD4 and CD8 T-cell response ex vivo.15 Young adults have a higher percentage of VZV-specific effector memory (EM) cells than elderly adults.15 We also demonstrated that the frequency of VZV-specific CD4 and CD8 EM T cells was inversely correlated with age and that VZV-reactive CD8 EM T cells from renal transplant recipients were impaired in peripheral blood.15

The protective effect of VZV-specific antibodies is considered limited,17,18 but memory B cells and plasma cells are responsible for the long-term persistence of humoral immunity.19 The antigen-specific B-cell enzyme-linked immunospot assay (ELISpot) is a robust tool to determine the frequency of antigen-specific antibody-secreting B cells.20

Our study had 2 aims: first, the incidence and severity of HZ after lung transplantation was investigated; and second, the frequency of systemic virus-specific B cells and naïve, central memory (CM) and EM CD4 and CD8 T cells were studied before and after HZ infection.

Methods

This study was conducted according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients included in the study.

Study population

This study included 119 lung transplant recipients who received a transplant between April 2002 and September 2014 at Erasmus MC (Rotterdam, The Netherlands). All patients were analyzed for VZV polymerase chain reaction (PCR) DNA in plasma/serum or blister fluid till March 15, 2015.

Peripheral blood mononuclear cells (PBMCs) were available from 5 patients before and after HZ infection to study VZV-specific B-cell and T-cell memory responses. The memory responses were compared with 5 patients who did not develop post-transplant HZ during follow-up of at least 3 years. The patients were matched for age, time after transplantation, pre-transplant donor/recipient cytomegalovirus (CMV) serology, and immunosuppressive load. Immunosuppression was not routinely tapered during HZ (Table 1).

Treatment

All recipients received 500 mg methylprednisolone intravenously in the operating room before reperfusion of each donor lung, followed by 100 mg after arrival in the intensive care unit, and 25 mg every 6 hours post-operatively. From 4 days to 6 months after transplantation, oral prednisolone was gradually tapered from 30 to 10 mg/day. Anti-CD25 monoclonal antibodies (daclizumab; 1 mg/kg) were given as induction therapy on Day 0 and Day 10. From November 2009, basiliximab (20 mg) was given at Day 0 and Day 4.

Maintenance immunosuppression consisted of a triple regimen of tacrolimus, mycophenolate mofetil (MMF), and prednisolone. Tacrolimus was titrated from whole blood levels 15 ng/ml in the

| Table 1 Cytomegalovirus Mismatch and Immunosuppressive Load Before and After Herpes Zoster in Patients With and Without Herpes Zoster |

<table>
<thead>
<tr>
<th>With herpes zoster (n = 5)</th>
<th>Post-herpes zoster</th>
<th>Without herpes zoster (n = 5)</th>
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<tr>
<td>Pre-herpes zoster</td>
<td></td>
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<tr>
<td>CMV D/R</td>
<td>Tacro (mg/day)</td>
<td>MMF (mg/day)</td>
</tr>
<tr>
<td>-/–</td>
<td>2</td>
<td>500</td>
</tr>
<tr>
<td>-/+</td>
<td>9</td>
<td>2,000</td>
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<tr>
<td>-/–</td>
<td>5</td>
<td>1,000</td>
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<tr>
<td>+/-</td>
<td>8</td>
<td>500</td>
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<td>-/+</td>
<td>3</td>
<td>500</td>
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</table>

CMV D/R, cytomegalovirus mismatch between donor and recipient; MMF, mycophenolate mofetil; Pred, prednisolone; Tacro, tacrolimus.
first post-operative week to 5 ng/ml from 1 year after transplantation. MMF was tapered from 3 g/day in the first post-operative week to 1 g/day from 1 year after transplantation.

Recipients who received a transplant from a CMV-positive donor or recipients with a past CMV infection were treated with valganciclovir for 3 months until 2012 and from 2012 for 9 months. A CMV-negative recipient receiving a transplant from CMV-negative donor did not receive prophylactic therapy.

Herpes zoster

VZV infection was clinically diagnosed and confirmed by diagnostic VZV-specific PCR on plasma or serum and/or blister samples. Uncomplicated cutaneous HZ is defined as vesicles in 1 to 2 dermatomes. Disseminated HZ involves 3 or more dermatomes,21 and the analysis included complications such as cranial involvement and PHN. PHN was defined as persistent pain for more than 3 months12 that needed opiate.23

VZV serology

Serum immunoglobulin G (IgG) antibodies to VZV were determined by enzyme-linked fluorescent assay technology (bio-Mérieux, VIDAS, Lyon, France). Results are expressed as arbitrary units (AU)/ml serum.

Functional T-cell assay

Mature human moDC were generated from CD14+ cells stimulated with a cocktail of cytokines, as described recently.15 Mature moDCs were cocultured with VZV-infected and mock-infected MeWo cells.15 After 24 hours, the moDCs were used as autologous APCs.

T cells (CD3+ cells) were isolated from the CD14+ fraction.15 Autologous T cells were stained, as described recently.15 Briefly, tubes 1 and 2 contained 1 × 10⁶ T cells and 1 × 10⁶ autologous moDCs infected with VZV, and tubes 3 and 4 contained T cells and autologous mock-infected moDCs. The cells from tubes 1 and 3 were stained with anti-CD4, anti-CD45, and anti-CC-chemokine receptor 7 (CCR7). The cells from tubes 2 and 4 were stained with anti-CD8, anti-CD45, and anti-CCR7. Thereafter, the cells from all tubes were fixed and permeabilized, followed by incubation with anti-interferon (IFN)-γ.

The net percentage VZV-reactive T cells was determined by enumerating the number of IFN-γ-producing CD3⁰CD4⁰ and CD3⁰CD8⁰ T cells stimulated with autologous moDCs infected with VZV, minus the respective values obtained upon stimulation with autologous mock-infected moDCs, on the fluorescence-activated cell sorter Canto-II (Becton Dickinson).

VZV-specific B-cell ELISpot

Because of low frequencies in peripheral blood, memory B-cells need first to be activated and expanded in vitro by a polyclonal stimulus.24,25 Consequently, PBMCs (2 × 10⁶/ml) were stimulated with B-cell stimulus (U-CyTech biosciences, Utrecht, the Netherlands) in Roswell Park Memorial Institute-1640 culture medium (GlutaMax; Gibco, Carlsbad, CA) supplemented with 2 mmol/liter L-glutamine (Lonza, Verviers, Belgium), penicillin/streptomycin (Lonza), and 10% heat-inactivated and filtered fetal bovine serum (Lonza). After an incubation of 5 days at 37°C in 5% CO2, cells were washed twice and resuspended in culture medium.

Ninety-six–well filter plates with polyvinylidene fluoride (PVDF) membrane (Millipore, Darmstadt, Germany) were pre-treated with 25 μl of 70% ethanol and then washed twice with phosphate-buffered saline (PBS) before being coated with 50 μl of 50 μg/ml capture VZV antigen (varicella zoster grade 2 antigen; Microbix Biosystems Inc., Mississauga, ON, Canada) or 50 μl capture anti-human IgG (U-CyTech biosciences) to determine the spontaneous frequency of IgG-producing B cells, and finally, 50 μl PBS. Coated plates were incubated overnight at 4°C, washed 3 times with PBS, and blocked with 200 μl blocking buffer (U-CyTech biosciences). The blocking buffer was removed, after which 2 × 10⁶ cells or 1 × 10⁶ cells/well were added in triplicate in case of VZV spots and total IgG spots, respectively. Plates were incubated for 5 hours at 37°C in 5% CO₂. Thereafter, the cells were removed and the underdrain from the bottom of the plates was discarded and removed. The plates were washed 6 times with PBS containing 0.05% Tween-20 (PBST) on both sides of the PVDF membrane, and 100 μl diluted biotinylated detection antibody (U-CyTech biosciences) was added and incubated overnight at 4°C.

After a washing procedure with PBST, 100 μl diluted streptavidin-horseradish peroxidase conjugate (U-CyTech biosciences) was added to the wells for 1 hour at 37°C. The plates were washed 5 times with PBST, and 100 μl 3-amino-9-ethyl carbazole (AEC) substrate solution (U-CyTech biosciences) was added. After 45 minutes at room temperature in the dark, color development was stopped by thoroughly washing both sides of the PVDF membrane with ultra pure water (Milli-Q water; Millipore Corp., Bedford, MA). Spots were counted automatically by using a Bioreader 3000 ELISpot reader (Bio-Sys, GmbH, Karben, Germany). Data are presented as the percentage of VZV-specific B cells of the total IgG memory B cells in PBMCs.

Statistical analysis

The incidence of HZ was calculated for the whole cohort at risk during the study period. The number of HZ cases divided by person-time at risk is presented as number of cases per 1,000 PY. Fisher’s exact test was used to compare the patients with and without HZ at transplantation. The significance of the difference in VZV-specific T-cell and B-cell reactivity before and after HZ was analyzed by the 2-sided Wilcoxon signed rank test. Statistical analysis comparing patients with and without HZ was performed with the 2-sided Mann-Whitney U test for unpaired observations.

Results

HZ incidence in lung transplant recipients

A total of 131 adults underwent lung transplantation between April 2002 and September 2014 at Erasmus MC (Rotterdam, the Netherlands). To allow the onset of HZ, serum/plasma or blister fluids were analyzed for VZV PCR in patients who were at least 6 months after transplantation. Twelve patients died within 6 months after transplantation. Consequently, 119 patients (63 male and 56 female) were analyzed for VZV PCR. Patients were a median age of 54 years (range, 19–66 years), and the median follow-up was 2.5 years (range, 0.08–12.35). One patient, a Caucasian man who was VZV IgG negative before transplantation, developed primary VZV infection 1.2 years after transplantation at the age of 60 years. The widely disseminated
vesicular rash recovered after systemic acyclovir treatment for 2 weeks.

HZ developed in 17 patients (9 men, 8 women) after lung transplantation. The baseline characteristics of these patients are reported in Table 2. Patients were a median age of 59 years (range, 35–67 years) at onset of HZ, and 14 (82%) were older than 50 years. The crude incidence of HZ was 17 of 119 patients (14.3%). The incidence of HZ after transplantation was 38.2 cases per 1,000 PY. HZ developed 1.3 years (range, 0.08–3.8 years) after transplantation (Figure 1). HZ occurred in 5% of the at 0.6 years after transplantation and in 10% at 1.4 years. The overall HZ incidence rate was 19% (Figure 1).

Patients who developed HZ after transplantation were significantly older at transplantation than patients without HZ after transplantation (Table 2; p = 0.01). No difference was found among the remaining general parameters such as gender, type of lung transplant (single or double), underlying disease, and CMV status (Table 2).

### Severity of HZ

HZ was localized in 12 patients, and they recovered after treatment with valacyclovir or ganciclovir. Three of those patients (17.6%) suffered from PHN and were treated with opiates for 3 to 7 months. Five patients (29.4%) experienced a disseminated HZ after transplantation without PHN. In the first patient, the cranial nerves C2-C5 were involved. The patient was treated with intravenous ganciclovir but died 6 days after onset of HZ. In 1 patient, 4 thoracic dermatomes were involved, but all vesicles disappeared after 2.5 weeks of treatment with valacyclovir. One patient with disseminated HZ recovered after 3 days of intravenous acyclovir, followed by 3 weeks valacyclovir. In the fourth patient, the left thoracic part, shoulder, and neck were involved. The patient was treated with intravenous acyclovir and oral valacyclovir and recovered. The last patient had a vesicular rash from the back to the abdomen that was successfully treated with valacyclovir for 2 weeks.

### VZV-specific T-cell and B-cell reactivity

VZV-specific T-cell reactivity was expressed as the percentage IFN-γ–producing VZV-reactive T cells identified by flow cytometric analysis ex vivo on blood-derived T cells. No difference was found in the naïve CD4 and CD8 T-cell population (Figure 2). The VZV-specific memory CD4 and CD8 T-cell response increased after HZ to significantly higher levels than in patients without HZ (p = 0.03, Figure 2). This increment in the CD4 T-cell memory population was mainly due to the CD4 EM (p = 0.02) T cells and was restricted to CM (p = 0.02) and EM (p = 0.03) T cells in the CD8 memory population (Figure 3).

The frequency of VZV-specific IgG-producing B cells was determined by ELISpot assay, and spots were counted

### Table 2  Clinical Characteristics at Lung Transplantation of Patients With and Without Herpes Zoster After Transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>With HZ (n = 17)</th>
<th>Without HZ (n = 102)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56 (35–67)</td>
<td>53 (19–66)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age ≥50 years</td>
<td>14 (82)</td>
<td>62 (55)</td>
<td>0.11</td>
</tr>
<tr>
<td>Sex Male</td>
<td>9</td>
<td>54</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex Female</td>
<td>8</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Type of lung transplant</td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Single</td>
<td>5</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td>12</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>8 (47)</td>
<td>45 (44)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>2 (12)</td>
<td>23 (23)</td>
<td>0.52</td>
</tr>
<tr>
<td>Non-cystic fibrosis bronchiectasis</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Interstitial lung diseases</td>
<td>5 (29)</td>
<td>31 (30)</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>2</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Extrinsic allergic alveolitis</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease related</td>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>2 (12)</td>
<td>2 (2)</td>
<td>0.10</td>
</tr>
<tr>
<td>CMV serostatus pre-transplantation Donor negative/recipient negative</td>
<td>6 (35)</td>
<td>27 (26)</td>
<td>0.56</td>
</tr>
<tr>
<td>Donor negative/recipient positive</td>
<td>6 (35)</td>
<td>29 (28)</td>
<td>0.57</td>
</tr>
<tr>
<td>Donor positive/recipient negative</td>
<td>3 (18)</td>
<td>20 (20)</td>
<td>1.0</td>
</tr>
<tr>
<td>Donor positive/recipient positive</td>
<td>2 (12)</td>
<td>26 (25)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; HZ, herpes zoster.

*Continuous data are shown as median (range) and categoric data as number (%).
on a Bioreader. The percentage of VZV-specific IgG-producing cells increased after HZ to a higher percentage than in patients without HZ \((p = 0.06, \text{Figure 4A})\). Remarkably, the percentage of VZV-specific IgG-producing cells and the IgG titer both decreased after HZ (Figure 4A and B) in 1 patient. Her VZV IgG titer was only increased 1 week after HZ; thereafter, the titer dropped below the level before HZ. In addition, her VZV-specific CD4\(^+\) memory T cells (both CM and EM) increased after HZ, whereas her VZV-specific CD8\(^+\) memory T-cell response (EM) decreased after HZ.

### Discussion

In immunocompetent patients, HZ is considered as a self-limited, localized skin infection that could be complicated by PHN. In contrast, immunocompromised patients

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**Figure 1** Percentage of lung transplant recipients free from herpes zoster after transplantation.

**Figure 2** Percentage of naïve (A) CD4\(^+\) T cells and (B) CD8\(^+\) T cells (CD45RO\(^-\)) and percentage of total memory (C) CD4\(^+\) T cells and (D) CD8\(^+\) T cells (CD45RO\(^+\)) within the CD3\(^+\) T-cell population from lung transplant recipients with and without herpes zoster (HZ). IFN, interferon; VZV, varicella zoster virus.
(e.g., transplant recipients) are at risk of severe cutaneous and visceral disseminated disease.26 The increased risk of HZ in transplant recipients is mainly due to decreased cellular immunity to VZV compared with healthy individuals.15

The incidence of HZ was 1 to 4 cases per 1,000 PY in healthy individuals aged 40 to 50 years and 7 to 8 cases per 1,000 PY in those aged 50 to 70 years.5 We found a significantly higher incidence of HZ (38.2 cases/1,000 PY) in our lung transplant cohort than in aged-matched individuals. The crude incidence of HZ was 14.3%, and the overall incidence of HZ was 19% in our population. PHN occurred in 17.3% of the patients, and 29.4% had

Figure 3 Percentage of varicella zoster virus (VZV)-specific (A, C) central memory (CM; CD45RO+CCR7+), (B, D) effector memory (EM; CD45RO–CCR7–), and (E) EMRA (CD45RO–CCR7–) cells within the (A, B) CD4+CD45RO+ and (C, D, E) CD8+CD45RO+ population from lung transplant recipients with and without herpes zoster (HZ). CCR, CC-chemokine receptor.

Figure 4 (A) Varicella zoster virus (VZV)-specific immunoglobulin G (IgG) enzyme-linked immunospot assay representing the VZV-specific IgG-producing B cells. Data are presented as the percentage VZV-specific B cells of the total frequency of IgG-producing cells in peripheral blood mononuclear cells. (B) VZV-specific IgG antibody responses. Data are expressed as arbitrary units (AU)/ml serum.
disseminated HZ infection, 1 of whom died 6 days after HZ presentation.

Only a few studies have described the incidence of HZ after lung transplantation. A high incidence of HZ was found in a cohort of 239 transplant recipients (55.1 cases/1,000 PY). These incidence rates are even higher than the rates from our present study (5.8% at 1 year, 18.1% at 3 years, and 20.2% at 5 years), only 2 had disseminated disease, and PHN developed in 20%. Among 198 lung transplant recipients described by Fukus et al., 23 had HZ (crude incidence, 11.6%), of whom 18 had HZ in a single dermatome, 4 had disseminated cutaneous infection, 1 had visceral involvement, and PHN was found in 26%.

These higher incidences may be caused by short-time use of anti-viral prophylaxis and a higher dose of the immunosuppressive regimen. Only 3 months of antiviral CMV prophylaxis was given in the first study, and a relative high target trough level of tacrolimus (8–12 ng/ml) combined with 1.5 g MMF and prednisone as maintenance therapy was given in the other study.

Gourishankar et al. described a crude incidence of 15.1% after lung transplantation. One study of 11 lung transplant recipients who required hospitalization to treat HZ complications described 4 patients who died early after the diagnosis of HZ.

VZV-specific T cells have been studied in peripheral blood, but only 1 study analyzed VZV-specific T cells after HZ infection. The present study found an increased frequency of VZV-specific CD4 and CD8 memory T cells in patients who experienced HZ after lung transplantation. Schub et al. reported a significantly elevated percentage of cytokine-producing VZV-reactive CD4 T cells in individuals during HZ compared with controls. After 4.3 months of follow-up, the frequency significantly decreased; however, the CD8 T-cell response was not determined. These authors also showed that the VZV IgG titer was high during HZ and decreased during follow-up in some patients. This could clarify the drop in B-cell reactivity of 1 of our patients. Our data should be confirmed in a larger cohort of lung transplant patients.

Prophylactic CMV therapy by anti-virals after transplantation could reduce the risk of HZ. Ko et al. demonstrated that short anti-CMV prophylaxis (< 3 months) was associated with HZ development after kidney transplantation. However, multivariate analysis revealed that CMV prophylaxis was not independently associated with HZ. In addition, no difference in risk for VZV infection was found between prophylactic and preemptive CMV strategies. The present study found no correlation with CMV prophylaxis and HZ. From the 17 patients who developed HZ, 6 patients did not receive CMV prophylaxis (i.e., patient and donor were both CMV negative), and from the 102 patients who did not develop HZ, 27 patients did not receive CMV prophylaxis ($p = 0.56$).

Vaccines to prevent HZ and its complications include the live-attenuated VZV vaccine (Zostavax; Sanofi Pasteur MSD; Lyon Cedex, France) and a new alternative vaccine consisting of an single VZV glycoprotein (gE) in an AS01 adjuvant system E (HZ/su). Studies have demonstrated that T-cell reactivity to VZV is mainly mediated by CD4 T-helper 1 cells and not by CD8 T cells after Zostavax vaccination. The difficulty of identifying VZV-specific CD8 T cells can be a result of the APC system used. We used autologous matured moDC as APCs to simultaneously enumerate and phenotype VZV-reactive CD4 and CD8 T cells. Consequently, we demonstrated that VZV-reactive memory CD4 T-cells are not only increased after HZ infection but also CD8 T cells. Therefore, our study highlights the importance of studying both the VZV-reactive CD4 and CD8 T cells after a vaccine to prevent HZ. Because of the small number of patients included, the importance of VZV-reactive memory T-cell and B-cell reactivity should be confirmed in larger future studies, and especially, the control group should be extended.

In summary, HZ is a frequent and serious complication after lung transplantation that may increase the VZV-specific memory B-cell and T-cell responses despite the immunocompromised status of the patients.

Disclosures statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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References