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Prevalence of VZV Reactivation and Effectiveness of Vaccination with Recombinant, Adjuvanted Zoster Vaccine in Allogeneic Hematopoietic Stem Cell Recipients-A Single-Center Analysis.

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Posted Date: 19 March 2025

doi: 10.20944/preprints202503.1396.v1

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 doi:10.20944/preprints202503.1396.v1

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Prevalence of VZV Reactivation and Effectiveness of Vaccination with Recombinant, Adjuvanted Zoster Vaccine in ALLOGENEIC hematopoietic Stem Cell Recipients-a Single-Center Analysis

Ewa Karakulska-Prystupiuk *, Magdalena Feliksbrot-Bratosiewicz, Maria Król, Agnieszka Tomaszewska, Wiesław Wiktor Jędrzejczak and Grzegorz Władysław Basak

Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Banacha 1a Str, 02-097 Warsaw, Poland

* Correspondence: ewa.karakulska-prystupiuk@wum.edu.pl; Tel. +48225991436, Fax: +48225991418

Abstract: Background: Secondary immunodeficiencies in allo-HSCT (allogeneic hematopoietic stem cell transplantation) recipients increase the risk of viral reactivation, making vaccinations a vital issue. There is a paucity of data on the use of recombinant vaccine against herpes zoster (RZV) after allo-HSCT. **Methods**: The analysis included 149 recipients of allo-HSCT, transplanted in 2012-2022, mainly due to hematological malignancies (>95%). RZV was used from 2021 to 2023 according to the current recommendations of ACIP. The ELISA method was used to assess the VZV IgG antibody titers. **Results**: VZV reactivation was diagnosed in 49 out of 149(33%) patients before vaccination, including 5(3%) patients with reactivation within the first year after transplantation and the remaining 44(30%) within the subsequent three years. At that time majority of patients were not receiving acyclovir prophylaxis. The most common clinical manifestation of reactivation was involvement of intercostal nerves diagnosed in 40(81%) patients. Twenty-one recipients (median age: 41) received two doses of RZV (at median time-34 months after transplantation, range 12-84 months), the majority of them at an interval of 1 month. The serological post-vaccination response was confirmed in 12 recipients with a ratio of 2.38- 8.3 (median 5.095). The median number of total CD3+CD4+cells in vaccinated patients was 451/µl. Despite vaccination, four patients (19%, three with confirmed serological response) developed herpes zoster. **Conclusions**: Herpes zoster occurred mainly in the late period after allo-HSCT after completion of acyclovir prophylaxis in over 30% of recipients. The preliminary results indicate that RZV vaccination after allo-HSCT is safe but may have limited effectiveness.

Keywords: Recombinant adjuvanted herpes zoster vaccine (RZV); herpes zoster (HZ); allogeneic hematopoietic stem cell transplantation (allo- HSCT); secondary immunodeficiency (SID)

1. Introduction

Recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT), especially these with graft-versus-host disease (GvHD), constitute a unique group of patients with secondary immunodeficiency (SID). Ablation of the hematopoietic system and damage to lymphopoietic organs due to toxic conditioning chemo-radiotherapy before transplantation leads to the impairment of cellular and humoral immunity. Restoring the total efficiency of the immune system is a multi-stage process spread over time. Cellular immunity deficiencies in allo-HSCT recipients significantly increase the risk of viral infections.

Varicella zoster virus (VZV) is a human alpha herpes virus surviving latent in ganglionic neurons and reactivating to produce herpes zoster (HZ, shingles). According to literature data, over 90% of the world population harbors latent VZV. At least 50% of infected individuals will reactivate

 doi:10.20944/preprints202503.1396.v1

this virus by 85 years of age to develop zoster. During reactivation, VZV spreads transaxonally but in immunosuppressed patients, may also be detected in peripheral blood mononuclear cells(PBMCs, which promote its dissemination)[1-5]. Long-lasting postherpetic neuralgia may be an essential complication in many recipients. The first objective of our study was to assess the incidence of HZ in recipients after HSCT.

Vaccination is a vital way to prevent symptomatic infection in HSCT recipients. However, the response to immunization in these SID patient populations may not be sufficient. There are two zoster vaccines: a live-attenuated vaccine, which is contraindicated in this setting, and the recombinant glycoprotein E vaccine. The efficacy of the recombinant HZ vaccine after autologous stem cell transplantation has been documented [6], but still the data on its use after allo-HSCT are limited. The Advisory Committee on Immunization Practices (ACIP) does not explicitly comment on these patients, choosing to await additional information [6-12]. Therefore, we considered it important to report our experience with recombinant vaccine against herpes zoster in this patient population.

2. Materials and Methods

2.1. Study Population

It is a retrospective analysis of patients after allo-HSCT performed in years 2012-2022 remaining under care of the Outpatient Service in single transplantation center. All patients signed written consent to receive vaccinations.

2.2. Allo-HSCT

Type of conditioning was chosen at the responsible physician's discretion and depended on the underlying hematological disease. Immunosuppressive treatment (GvHD prophylaxis) was a combination of a calcineurin inhibitor (cyclosporin or tacrolimus) and an antiproliferative drug-either a short course of methotrexate or mycophenolate mofetil. All patients with unrelated or mismatched donors received anti-T cell globulin (2,5-5 mg/kg daily) in a conditioning regimen for 2–3 days prior transplantation. Diagnosis and grading of acute and chronic GvHD were performed based on clinical symptoms and/or biopsies according to established criteria. Grading of acute GvHD was performed according to the Glucksberg score, while the severity of chronic GvHD according to National Institutes of Health (NIH) Consensus Criteria 2014 [13-15].

All patients received anti-infective prophylaxis, including prophylactic antiviral treatment with acyclovir (400-800 mg twice daily) or with letermovir (24-480mg daily) for the first 100 days after allo-HSCT followed by acyclovir (in doses as above) or valgancyclovir (in a case of CMV reactivation, in doses adjusted for creatinine clearance). Immunosuppressive therapy was discontinued after 6–8 months following allo-HSCT if there was no significant GvHD. All patients who have been receiving immunosuppressive therapy due to cGvHD were advised to continue acyclovir treatment [7,12].

2.3. Types and Doses of Vaccine

Recombinant adjuvanted herpes zoster vaccine (RZV) was used in 2021-2023 in patients according to the current recommendations of the Advisory Committee on Immunization Practices (ACIP) for Immunocompromised Adults aged ≥19 years [10]. Vaccination included two doses of the vaccine given 1-2 months apart. The follow-up for efficacy was 1-3 years [8-11].

2.4. Methods

The anti-VZV (IgG) ELISA test manufactured by Euroimmun was primarily used. Ratio≤0.8 was considered negative, 0.8-1.1equivocal, and >1.1positive.

In three patients direct chemiluminescentimmunoassay (CLIA) was used with titers≥ 150mIU/ml considered as positive result.

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Peripheral blood lymphocyte subpopulations were analyzed using flow cytometry. The reference intervals were 309-1139 cells/μL for CD3+4+ cells, 137-823 cells/μL for CD3+8+ cells, 70-460 cells/μL for NK cells, and 80-430 cells/μL for CD19+ B-lymphocytes, and 1,0–5,0 for CD4+ to CD8+ ratio. Post-vaccination complications were graded according to CTCAE5.0 criteria. Patients gave written consent to the intervention.

3. Results

3.1. Patients

The analysis included one hundred forty-nine patients, 85(57%) males, with median age of 47 years (range 18–73) at allo-HSCT. For twelve patients, it was the second allo-HSCT. The most prevalent diagnoses were acute myeloid leukemia (AML)- 55%, then myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia (ALL)- both 11.5%.

Baseline patients' characteristics are shown in Table 1.

Table 1. Baseline patients' characteristics.

	Number of patients	Share of the total (%)
Gender		
Male	85	57
Female	64	43
Age in years		
18-40	57	38
40-60	74	49
>=60	18	13
Diagnosis		
AML	82	55
MDS	17	11.5
ALL	17	11.5
AA	6	4
MPN	14	9
Lymphoma	13	9
Conditioning		
MAC	104	70
NMA	5	3
RIC	40	27
Donor		
MRD	49	33
MUD	83	56
MMUD	12	8
Haplo	5	3
Acute GvHD		
Grade 1-2	40	27
Grade 3-4	24	16
Chronic GvHD		
Mild	17	11
Moderate	33	22
Severe	34	23

(AA- aplastic anemia, AML- acute myeloid leukemia, ALL- acute lymphoblastic leukemia, GVHD- graft versus host disease, MAC- myeloablative conditioning, MDS- myelodysplastic syndrome, MPN- myeloproliferative neoplasm, MMUD- mismatched unrelated donor, MRD- matched related donor, MUD- matched unrelated

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donor, NMA- non-myeloablative conditioning, RIC- reduced intensity conditioning, GvHD- Graft-versus-Host Disease).

3.2. Transplantations

HLA-identical siblings were used for 49(33%) patients, matched unrelated donors for 83(56%), mismatched unrelated donors for 12(8%), and haploidentical related donors for 5(3%). There were 104(70%) patients, who received myeloablative conditioning (MAC), 40(27%) reduced-intensity conditioning (RIC), and 5(3%) non-myeloablative conditioning (NMA).

3.3. GvHD

Sixty-four(43%) patients suffered from acute and 85(57%)- chronic GvHD. Altogether 67(45%) patients required chronic immunosuppressive therapy (mostly calcineurin inhibitor) because of moderate or severe chronic GvHD.

The prevalence of VZV reactivation in the entire group before vaccination:

VZV reactivation was diagnosed in 49 out of 149(33%) patients, including 5(3%) patients with reactivation within the first year after transplantation and the remaining 44(30%) within the subsequent three years.

At this time, majority patients no longer received acyclovir prophylaxis, including five patients who stopped recommended prophylaxis despite receiving immunosuppressive treatment (3 - due to chronic GvHD, 2 - for its prevention). The most common clinical manifestation of VZV reactivation involving intercostal nerves was diagnosed in 40(81%) patients. The remaining patients had unusual locations, including 3 patients with cranial nerve involvement, 2- with ophthalmicus, 2- with ulnar nerves, 1- with sacral plexus involvement, and 1- with a disseminated form of herpes zoster (HZ, diagnosed in a patient with Wiskott-Aldrich syndrome). Four patients required hospitalization: one due to a disseminated herpes zoster, *one-* ophtalmicus, and two others- for infectious complications (1- pneumonia, 1- bronchitis). Postherpetic neuralgia was an essential complication in many of them. There was no intercurrent infection with Epstein-Barr virus and cytomegalovirus in patients with HZ, but in two of them, shingles appeared 24 hours after the SARS-CoV2 mRNA vaccine.

The assessment of the vaccinated group:

Twenty-one recipients (median age: 41) received two doses of RZV (median time 34 months after transplantation (range, 12-84 months). Patients were vaccinated when the vaccine became available which resulted in variability in time duration between transplantation and vaccination. There were 11-seronegative, 2- equivocal, 1-seropositive, and 7-unassessed patients before vaccinations (all with a history of chickenpox in childhood). Eighteen of them have been vaccinated at an interval of 1 month, and the remaining three- at an interval of 2 months. Several patients complained about mild pain, erythema, swelling, or fatigue- CTCAE grade 1 after injection.

During vaccination, four patients have been receiving chronic immunosuppressive treatment due to severe (3 patients) and moderate (1 patient) chronic cGvHD. The serological post-vaccination response (measured 2-3 months after vaccination) was confirmed in 12(57%) recipients with a ratio of 2.38- 8.3 (median 5.095). Despite vaccination, four patients developed HZ. These patients were not receiving immunosuppressive therapy at the time of disease onset. One of them, initially with myelodysplastic syndrome, had received rituximab a year earlier for PRCA (pure red cell aplasia) after transplantation. Three others underwent transplantation for lymphoid malignancies (2 –B-cell ALL, 1 - DLBCL), including one who required IgG supplementation until 3 months before disease onset. Three of these patients had positive serological response to vaccinations.

The median count of total blood cells in the vaccinated group, in 1-4 months before vaccination was 451 (range 309-1139) for CD3+4+, 855 (range 137-823) for CD3+8+, 406 (range 70-460) for CD19+ and 211 (range 80-430) for NK cells. None of the vaccinated patients had a decreased count of total CD3+8+, and CD19+ below LLN. All but three (86%) had a lower CD4/CD8 ratio. Six vaccinated patients had the absolute count of total CD3+CD4+cells below LLN, including two, who developed

 doi:10.20944/preprints202503.1396.v1

clinical disease. Three vaccinated patients had the absolute count of total NK cells below LLN, including one with clinical disease. Vaccinated patients' characteristics are shown in Table 2.

Table 2. Vaccinated patients' characteristics (patients who developed herpes zoster were marked in bold).

	Age	Gender	Diagnosis	Time to first vaccine dose after HSCT (months)	Ratio value for VZV IgG before and after vaccination (or * titer in mIU/ml)		CD4/µL N[309-1139]	CD8/µL N[137-823]	CD19/µL N[70-460]	NK/µL N[80-430]	CD4/CD8 N[1.0-5.0]
					before	after					
1	22	F	AML	12	0.64	7.07	616	535	227	211	1.2
2	34	M	AML	18	0.52	8.16	220	642	406	406	0.3
3	53	F	CML	36	1.15	7.43	135	450	83	45	0.3
4	**40**	**F**	**MDS**	**31**	**No data**	**2.4**	**266**	**931**	**418**	**228**	**0.3**
5	33	F	MDS	35	0.25	4,28	672	496	160	208	1.4
6	**41**	**M**	**DLBCL**	**18**	**0.77**	**3.09**	**360**	**1400**	**1240**	**840**	**0.3**
7	*38*	*M*	*PTCL*	*60*	*No data*	*4.05*	*1161*	*826*	*258*	*258*	*1.4*
8	50	M	CML	14	142*	6.86	475	1425	1536	144	0.3
9	*54*	*F*	*AML*	*84*	*No data*	*3.44*	*312*	*396*	*408*	*72*	*0.8*
10	67	F	AML	61	No data	3.16	260	900			0.3
11	50	M	AML	34	0.65	3.92	315	1095			0.3
12	67	M	AA	48	No data	5.91	223	594	127	106	0.4
13	22	F	AML	35	0.98	2,38	419	855	346	164	0.5
14	36	F	ALL	29	0.72	No data	469	2180	110	83	0.2
15	52	F	AML	12	0.44	No data	658	2632	799	423	0.3
16	22	F	AML	17	0.7	8.3	451	354			
17	*48*	*F*	*AML*	*48*	*No data*	*No data*	*718*	*800*	*773*	*359*	*0.9*
18	*66*	*M*	*MDS*	*14*	*No data*	*1041**	*654*	*2755*	*607*	*467*	*0.2*
19	**23**	**M**	**ALL**	**47**	**1.01.**	**7.57**	**266**	**714**	**336**	**42**	**0.4**
20	**26**	**F**	**ALL**	**26**	**90***	**538***	**783**	**1276**			**0.6**
21	66	F	AML	39	0.86	6.39	842	1427	421	356	0.6

italics – patients treated with immunosuppressive therapy due to GvHD at the time of vaccination.

4. Discussion

Secondary immunodeficiencies observed in HSCT recipients increase the risk of VZV reactivation, according to the Hope-Simpson hypothesis that a person's immune status determines their likelihood of developing HZ [1]. Pre-, peri- and post-transplant factors, especially the multi-stage immune reconstitution, lead to humoral and cellular deficiencies that may promote the occurrence of HZ.

Another critical issue may be immunosenescence- a documented factor that causes virus-specific cellular immunity to wane with age [2-4]. Faster aging lymphoid-biased HSCs (Ly-HSCs) in post-HSCT don't efficiently generate lymphoid progeny and can weaken VZV-specific CMI (T-cell–mediated immune) response [15-19].

The first objective of our study was to assess the incidence of HZ in recipients after HSCT, and VZV reactivation was diagnosed in 33% of patients within the first four years after transplantation. Apparently, acyclovir prophylaxis during the first year post-transplantation, used according to the EBMT guidelines, reduced the frequency of VZV reactivation during this time. Still, the frequency of the disease in the later period after transplantation (without prophylaxis) was a significant challenge [7,12].

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According to literature data, a delayed increase in VZV reactivation may be explained by the underlying immunosuppression rather than a possibility of a "rebound" effect. However, randomized studies suggest that subclinical VZV reactivation (endogenous and exogenous amplification) continues independently of acyclovir prophylaxis and that antigen exposure is sufficient for VZV-specific immune reconstitution [20, 21].

The frequency of VZV reactivation varies depending on the transplant centre; it was reported to be between 20% and 53%, with an increasing frequency in the subsequent years (5% in the first year after HSCT, 21% in the 2ndyear, 22.9% in the 3rdyear, and 37% in the 5thyear). This rate of VZV reactivation in the analyzed group of HSCT recipients is significantly increased compared to the people of similar age in non-HSCT population, where the frequency is reported to be only 7-8‰ [1,4,22].

Nineteen percent of our patients had unusual clinical manifestation of VZV reactivation, including two, who developed ulnar nerve involvement after COVID-19 vaccination. VZV reactivation is a known potential adverse event for all COVID-19 vaccines [23]. However manifestation involving dermatomes of the vaccinated arm have not yet been described.

Four (8.1%) of our patients required hospitalization- a significantly higher number compared to the non-HSCT population (0.05‰) [22]. One of these cases was a man initially suffering from primary immunodeficiency (PID) who developed severe disseminated HZ. It is known that PID recipients may experience poorer T and B cell reconstitution after allo-HSCT, which may complicate the course of the disease [19, 26].

It is also worth mentioning that having shingles exposes this vulnerable group of patients to the risk of long-term transplant complications, such as increased risk of secondary cancer, stroke, myocardial infarction, and, crucially - persistent postherpetic neuralgia [24-34].

The second part of our study was devoted to the problem of vaccination with recombinant, adjuvanted zoster vaccine.

The efficacy of this vaccine in the analyzed group, measured by the number of HZ occurrences after vaccination, was over 80%. There is not much data on the effectiveness of the recombinant vaccine against herpes zoster after allo-HSCT. In a randomized clinical trial of auto-HSCT recipients, the efficacy of vaccines was 63.8%. In contrast, in a single-center prospective study of allo-HSCT recipients published by Baumrin et al., it was 97.5% [27]. The comparison of the obtained results is difficult, considering different vaccination schedules and different elapsed times between transplantation and the start of vaccination.

It is essential to determine the optimal time to administer vaccinations, considering the immune reconstitution, especially the count of CD4+ and CD8+ effector and memory T cells (because of their importance in T-cell–mediated VZV-immune (CMI) responses). None of the analyzed vaccinated patients had a decreased count of total CD3+8, whereas six of the CD3+4+ count was diminished. Among four patients who developed HZ, two had absolute CD3+CD4+ counts below the LLN, and one had a deficiency of NK cells.

According to the literature, detection of VZV memory T cells is usually possible by 9 to 12 months after HCT, while VZV recurrence correlates significantly with their deficiency [28].

Potential clinical efficacy of VZV subunit vaccines containing glycoprotein E, in HCT recipients is related to driving VZV-specific CD4+ and CD8+ T cell reconstitution [4]. Therefore, having a CD4+ T cell count ≥200 cells/μL may be necessary for successful vaccination [4].

An insufficient count of NK cells may also have great importance in the susceptibility of HZ. Nonspecific antiviral immunity, especially IFN-α and granulysin made by NK, has direct antiviral activity against VZV and enhances the early destruction of VZV-infected cells.

In our analysis, we used serological testing to check post-vaccination responses, aware that no data for immunocompromised patients could guide cut-offs for positive antibody titers. The serological post-vaccination response was confirmed in 12(57%) recipients, including four, who developed overt disease despite vaccinations. Three of these four patients had initially lymphoid malignancies before transplantation, and the fourth- had been treated with rituximab after allo-HSCT

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(due to pure red cell aplasia). According to the literature, patients with B-cell malignancies are particularly vulnerable to total and/or functional post-transplant hypogammaglobulinemia, which results from disease-related effects and treatment-related side effects [27, 30]. Functional immunoglobulin deficiencies in these recipients may play a role in the expected efficacy of vaccinations in post-transplant care.

It is worth mentioning that four vaccinated patients with cGvHD did not develop clinical zoster disease. They were in the chronic phase, on a stable, partially reduced doses of immunosuppressive therapy, and all had regenerated lymphocyte subpopulations.

Due to a small group of recipients (the RZV vaccine was not reimbursed for allo-HSCT recipients in Poland at that time) and a short follow-up period, our results are preliminary. Still, they may contribute to the discussion around the validity and effectiveness of vaccinations against VZV in these SID patients.

In conclusion, Herpes zoster is a common complication after allo-HSCT and occurs in over 30% of recipients, mainly in the late period after transplantation after completion of acyclovir prophylaxis. The preliminary results indicate that RZV vaccination after allo-HSCT is safe but may have limited efficacy, especially in patients transplanted for lymphoid malignancies.

Authors' Contribution: All authors critically revised the paper and agreed to the published version of the Manuscript. Conceptualization: E.KP, W.W.J., G.W.B., Methodology: : E.KP, M.FB, M.K, Validation: E.KP, W.W.J. G.W.B, Formal Analysis: E.KP, Investigation: E.KP, M.FB, M.K, Resources: E.KP, M.FB, M.K, A.T, W.W.J, G.W.B, Data Curation: E.KP, M.FB, M.K, Writing – Original Draft Preparation: E.KP, Writing – Review & Editing; E.KP, M.FB, M.K, A.T, W.W.J, G.W.B, Visualization: E.KP. Supervision: W.W.J, G.W.B, Project Administration: E.KP, W.W.J, G.W.B, Funding Acquisition: E.KP, G.W.B

Funding: This research received no external funding

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bioethics Committee of the Medical University of Warsaw No. AKBE/311/2024.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Acknowledgements: We thank all the patients, their families and the members of staff involved in their care.

Conflicts of Interest: The authors declare no conflict of interest.

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