The recombinant zoster vaccine is safe and tolerable in allogeneic hematopoietic stem cell recipients, does not increase rates of chronic graft versus host disease, and results in low rates of breakthrough herpes zoster

Safety and Reactogenicity of the Adjuvanted Recombinant Zoster Vaccine after Hematopoietic Stem Cell Transplantation

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Introduction

- Varicella zoster virus (VZV) reactivation is common after allogeneic hematopoietic stem cell transplantation (HCT) and is associated with high morbidity and mortality[1]
- Prolonged antiviral prophylaxis reduces incidence of VZV reactivation, yet risk remains after discontinuation, necessitating vaccination strategies[2,3,4]
- **The adjuvanted recombinant zoster vaccine (RZV) is now recommended for healthy adults >50 years old but has not yet been studied in this population[5]**

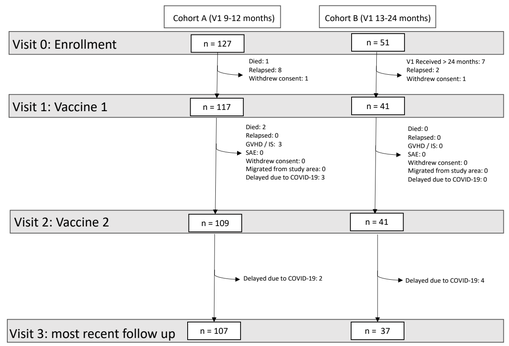
Objectives

- **Primary endpoint:** safety and reactogenicity of RZV after allogeneic HCT
- **Secondary endpoints:**
  - Incidence and severity of chronic graft versus host disease (GVHD) of RZV recipients compared to historical controls
  - Incidence rates of herpes zoster (HZ) in the vaccinated cohort

Methods

- **Single center prospective observational cohort study** of allogeneic HCT recipients >18 years old who were between 9-24 months after HCT. Subjects received 2 intramuscular doses of RZV separated by > 8 weeks and followed from December 2018-June 2020.
- **Safety and reactogenicity** were measured; solicited adverse events for 7 days, unsolicited adverse events for 30 days, and serious adverse events until study end
- **chronic GVHD, relapse, death, and HZ cases** were collected prospectively and compared to historical controls at our institution and to rates reported in the literature

Results: Participant Flow and Characteristics



- **150/158 (95%) completed vaccination series**

Participant Characteristics	Recombinant Zoster Vaccine No. (%)
Age (mean ± SD [range])	55.05 ± 13.83 [19-76]
Sex (%)	
Male	91 (58%)
Female	67 (42%)
Race (%)	
White	137 (87%)
Asian	7 (4%)
Black or African American	4 (3%)
Other	10 (6%)
Primary indication for transplant (%)	
AML	53 (34%)
MDS	29 (18%)
ALL	24 (15%)
MPD	12 (8%)
Anemia, Red cell disorder	9 (6%)
NHL	10 (6%)
Other[1]	21 (13%)
Regimen (%)	
Myeloablative	55 (35%)
Non-myeloablative	103 (65%)
Donor (%)	
Matched related	24 (15%)
Mismatched related	23 (15%)
Matched unrelated	87 (55%)
Mismatched unrelated	24 (15%)
Source of stem cells (%)	
Peripheral blood	118 (75%)
Bone marrow	37 (23%)
Cord blood	3 (2%)

Herpes Zoster and Vaccine Characteristics	Recombinant Zoster Vaccine No. (%)
VZV IgG (%)	
Positive	146 (92%)
Negative	9 (6%)
Indeterminate	3 (2%)
Herpes zoster prior to transplant (%)	
Yes	22 (14%)
No	135 (85%)
Unknown	1 (1%)
ZVL prior to transplant (%)	
Yes	29 (18%)
No	113 (72%)
Unknown	16 (10%)
Time from transplantation to V1, d median (IQR)	280.50 (267.0, 407.0)
Time between V1 and V2, d (IQR)	91.0 (70.0, 105.0)
Active chronic GVHD (%)	
At V1	60 (38%)
At V2[2]	61 (41%)
Systemic immunosuppression (%)	
At V1	112 (71%)
At V2	90 (60%)
Co-administered vaccines (%)	
At V1	148 (94%)
At V2	126 (84%)
Antiviral prophylaxis (%)[3]	
At V1	157 (99%)
At V2	147 (98%)

- **Many patients were vaccinated with active cGVHD (38-41%) and on immunosuppression (60-71%)**

Results: Safety and Efficacy

RZV Reactogenicity and Safety

Adverse events	Recombinant Zoster Vaccine[1] No. (%) [95% CI]
Any grade	139/151 (92.1) [86.5, 95.8]
Grade 3	49/151 (32.5) [25.1, 40.5]
Injection site adverse events[1]	
Any grade	131/150 (87.3) [80.9, 92.2]
Grade 3	28/150 (18.7) [12.8, 25.8]
General adverse events[2]	
Any grade	125/151 (82.8) [75.8, 88.4]
Grade 3	40/151 (26.5) [19.6, 34.3]
Unsolicited adverse events	
Within 30 days of vaccination	11/150 (7.3) [3.7, 12.7]
Related to trial intervention	6/150 (4.0) [1.5, 8.5]
Serious adverse events[3]	
Within 30 days of vaccination	2/150 (1.3) [0.2, 4.7]
Within total follow up period	2/150 (1.3) [0.2, 4.7]
Relapse of malignancy	13/158 (8.2) [4.5, 13.7]
Death	5/158 (3.2) [1.0, 7.2]

[1]Pain, redness, swelling

[2]Fever, gastrointestinal, myalgia, shivering, fatigue, headache

[3]SAE related to trial: metabolic acidosis and weakness resulting in hospitalization, fever resulting in hospitalization

Rates of Chronic GVHD, Relapse and Death in Peri-Vaccination Period

- **Incidence of cGVHD, relapse and death at 9, 12, 15 months were compared between Cohort A and historical controls adjusting for age, sex, HLA matching, stem cell source and GVHD prophylaxis medications.**
  - **cGVHD:** adjusted IRR 1.05 [CI 0.8-1.38]
  - **Relapse:** adjusted IRR 0.97 [CI 0.46-2.04])
  - **Death:** adjusted IRR 0.41 [CI 0.14-1.25]

HZ Case Rates and Characteristics

Recipient, No.	Confirmed cases of HZ, No.	Cumulative follow-up period, PY; median, d (IQR)[1]	HZ, IR / 1000 PY
Total Vaccinated Cohort[2]			
157	4	109.01; 263 (172, 350)	36.69
Modified Total Vaccinated Cohort[3]			
144	3	69.42; 281 (190, 354)	28.34
Participants who discontinued antiviral prophylaxis during study			
34	4	13.57; 113 (44, 204)	294.77

- Median 76.5 days (range 10-115) after V2
- Median 25.5 days (range 9-206) after d/c of antiviral ppx
- 0/4 patients on immunosuppression, 0/4 patients on antiviral ppx
- 3/4 dermatomal HZ, **1/4 death from disseminated VZV**

Conclusion

- **RZV was acceptable** with 95% of participants completing the vaccination series
- Solicited reactions were reported in the majority of participants and occurred more frequently than in healthy adults[6,7] but at similar rates to autologous HCT recipients[8]
- **Unsolicited AEs and SAEs related to the vaccine were infrequent and similar to other cohorts[6,7,8]**
- Many participants received RZV with active GVHD and/or immunosuppression, yet, there was **no increase in cGVHD, relapse, or death compared to historical controls**
- **There were low rates of breakthrough HZ** with incidence ratios similar to autologous HCT recipients[8]. Crude incidence was lower than reported in the allogeneic HCT literature[2,3,9,10, 11]
- **There was a fatal case of disseminated VZV** highlighting RZV's limitations
- **Immunogenicity studies and placebo-controlled trials are needed to determine vaccine response and efficacy** so that timing of RZV and its potential impact on discontinuation of antiviral prophylaxis can be determined

References

[1]Koc et al Biology of Blood and Marrow Transplantation, 2000, 6(1)
[2]Boeckh et al Blood, 2006, 107 (5)
[3]Erard et al Blood, 2007, 119 (8)
[4]Lee et al Journal of the Am Society of Blood and Marrow Transplantation, 2019, 25 (8)
[5]Dooling et al MMWR, 2018, 67 (3)
[6]Lal et al N Engl J Med, 2015, 372 (22)
[7]Cunningham et al, N Engl J Med, 2016 375 (11)
[8]Bastidas et al JAMA, 2019, 322 (2)
[9]Jamani et al Blood Advances, 2016, 1 (2)
[10]Seo et al Antiviral Research, 2017, 140

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