Safety and Tolerability of SARS-CoV-2 Emergency-Use Authorized Vaccines in Allogeneic Hematopoietic Stem Cell Transplant Recipients

Ali H, Ngo D, Aribi A, et al. *Transplantation and Cellular Therapy*. 2021.

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Disclosures

I have no relevant financial relationships with commercial interests pertaining to the content presented in this program.

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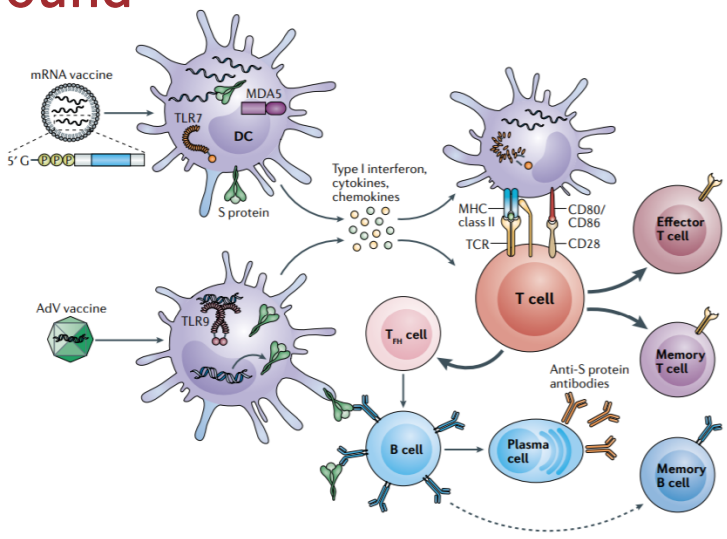
Learning Objective

Identify efficacy of SARS-CoV-2 vaccination and vaccine adverse events in patients receiving these vaccines following allogeneic hematopoietic stem cell transplant

Background



Teijaro J, et al. *Nat Rev Immunol*. 2021;21:195–197.

Background

- In patients with hematopoietic cell transplantation (HCT), infection is a leading cause of non-relapse mortality
- Immune system dysfunction following HCT
  - Conditioning with chemotherapy +/- radiation therapy leading to reduced cellular and humoral immune function
  - May take weeks for recovery of innate immunity, months to years for adaptive immune function recovery
- Patients with recent HCT or CAR-T cell therapy were excluded from initial SARS-CoV-2 vaccine trials
  - Applicability of these trial results

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Mehta R, et al. *Virulence*. 2016;7(8):901-916.
Ljungman P, et al. *Leukemia*. 2021; online.

Background

- Patients who have received hematopoietic stem cell transplant are at higher risk for severe outcomes when infected with SARS-CoV-2
  - Higher risk for ICU admission
  - Mortality rate of up to 28%
  - Development of lower respiratory tract disease
- Guidelines recommend waiting 3-6 months following HCT to administer most vaccines
  - Allow for recovery of B-cells and T-cells
  - Chronic graft-versus-host disease may further delay or inhibit recovery
    - Do not recommend delaying vaccination in these patients, have been shown to still have capacity to mount response

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Mehta R, et al. *Virulence*. 2016;7(8):901-916.
Ljungman P, et al. *Bone Marrow Transplant*. 2009;44:521-526.

Background

Purpose:

- To determine the safety and efficacy of the SARS-CoV-2 vaccines in patients who have received allogeneic hematopoietic stem cell transplant (HCT)

Objectives:

- Assess the rate of adverse events following vaccination
- Monitor frequency of new-onset graft-versus-host disease (GVHD)
- Evaluate incidence of SARS-CoV-2 positivity following vaccination

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Study Design & Methods

Design:

- Retrospective review

Methods:

- Patients identified via electronic medical records (EMR)
- Baseline labs drawn
  - Complete blood count with differential, serum creatinine, liver function tests
  - Changes in laboratory values evaluated for severity using CTCAE version 5
- Patients required to have physician follow-up at least 1 week after first vaccine dose

Analysis:

- Assessments within 40 days of second dose
- New or worsening GVHD determined by EMR review
- Determination of COVID-19 infection following vaccination

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Adverse Drug Event Definitions (CTCAE Version 5)

Grading	Hepatic Impairment	Thrombocytopenia	Neutropenia	Lymphopenia
Grade 1	AST/ALT 3x ULN (1.5-3x ULN if baseline abnormality), ALP 2.5x ULN (2.0-2.5x ULN if baseline abnormality)	Platelets <75,000/mm^3	Neutrophil count <1,500/mm^3	Lymphocyte count <800/mm^3
Grade 2	AST/ALT 3-5x ULN, ALP 2.5-5x ULN	Platelets 50,000-75,000/mm^3	Neutrophil count 1,000-1,500/mm^3	Lymphocyte count 500-800/mm^3
Grade 3	AST/ALT 5-20x ULN, ALP 5-20x ULN	Platelets 25,000-50,000/mm^3	Neutrophil count 500-1,000/mm^3	Lymphocyte count 200-500/mm^3
Grade 4	AST/ALT > 20x ULN, ALP >20x ULN	Platelets <25,000/mm^3	Neutrophil count <500/mm^3	Lymphocyte count <200/mm^3
Grade 5	N/A	N/A	N/A	N/A

AST = Aspartate aminotransferase
ALT = Alanine aminotransferase
ALP = Alkaline phosphatase

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CTCAE V5. US Department of Health and Human Services. 2017.

Eligibility

Inclusion Criteria

- 18 years of age or older
- Allogeneic hematopoietic stem cell transplant (HCT) recipients
- Received at least one dose of either Pfizer or Moderna mRNA vaccine post-HCT between December 2020 and April 2021

Exclusion Criteria

- None

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Endpoints & Analysis

Primary Endpoint:

- Frequency of adverse events (patient and laboratory reported)

Secondary Endpoints:

- Impact of vaccine administration on GVHD
- Incidence of infection with SARS-CoV-2 following vaccination

Analysis:

- Incidence of adverse reactions and SARS-CoV-2 infection
- Severity grading only available for laboratory adverse events
  - New or worsening GVHD – defined as addition of GVHD medications or increasing doses unrelated to therapeutic monitoring

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Population

Included **113** patients

- Median age of 66.5 years
- Study population 79% male
- Median of 588 days since transplant at time of vaccination (range, 100-11,004 days)
- Pfizer vaccine (BNT162b2) administered to 43.4% of patients
- Four patients with history of positive SARS-CoV-2 PCR test prior to vaccine

Baseline Characteristics	n=113 (%)
Primary diagnosis at HCT	
AML	51 (45.1)
ALL	9 (8.0)
MDS	20 (17.7)
Myelofibrosis	18 (15.9)
Other	15 (13.3)
Donor type	
Matched related	26 (23.0)
Matched unrelated	53 (46.9)
Mismatch unrelated	15 (13.3)
Haploidentical	19 (16.8)
Receiving immunosuppressants for GVHD	73 (65)
Corticosteroid use for GVHD	15 (13.3)

AML: acute myeloid leukemia
ALL: acute lymphoblastic leukemia
MDS: myelodysplastic syndrome

Results

Patient follow-up and documentation of adverse events:

- Median follow-up of 49 days for patients receiving both doses (range, 12-70 days)
  - 8 patients received only first vaccine dose
- 36 of 113 (31.9%) of participants responded to the survey
- Physician evaluation of adverse events
  - Reported in 16 patients receiving first dose, 12 patients receiving second dose

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Results

Most commonly reported adverse events

Adverse event	First Dose (n=113) n, (%)	Second Dose (n=105) n, (%)
Myalgia/Arthralgia	4 (7.7)	7 (14.6)
Fatigue	8 (15.4)	14 (29.2)
Pain at injection site	21 (40.4)	21 (43.8)

vomiting, diarrhea, headache, swelling/rash at injection site, axillary lymphadenopathy, and hypertension/tachycardia

Clinical laboratory adverse events

Adverse event	First Dose (n=113) n, (%)	Grade 3 or 4 adverse events
Hepatic Impairment	21 (18.6)	2 (1.8)
Neutropenia	15 (13.3)	4 (3.5)
Thrombocytopenia	13 (11.5)	4 (3.5)
Lymphopenia	10 (8.8)	4 (3.5)*

neutropenia and 2 of 4 patients with grade 3 or 4 thrombocytopenia were receiving active chemotherapy

- All patients with grade 3 lymphopenia had lymphopenia at baseline

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*No grade 4 lymphopenia reporte

Results

Graft-versus-host disease

- **Baseline**: chronic GVHD present in 45 patients (39.8%) **prior to** vaccination
- **New**: 13 patients reported new or worsening GVHD following

GVHD Location	New, n	Worsening, n
Skin	5	1
Oral	3	2
Gastrointestinal	3	1
Eye	2	1
Lung	1	0
Joints	0	1

SARS-CoV-2 Positivity

- Occurred in 2 patients following vaccination, asymptomatic
  - Both with history of infection, potential viral shedding

*GVHD well-controlled with symptom resolution or improvement for all patients by end of follow-up

Discussion Question

Which of the following potential mechanisms proposed by the authors do you think seems most likely to have led to the outcome of a lower rate of adverse events in this trial compared to those reported in the BBNT162b2 and mRNA-1273 registration trials?

a. Low survey response rate
b. Use of immunosuppressive therapies for prevention and treatment of graft versus host disease (GVHD)
c. Lack of normalized immune function to allow for immune mobilization following vaccination due to less than one year of elapsed time since hematopoietic stem cell transplant

Critiques

Strengths:

- Findings suggest adverse effect profile similar to general population
- Likely low risk for SARS-CoV-2 vaccination to cause new-onset GVHD
- Inclusion of large number of patients receiving immunosuppression for prevention/treatment of GVHD

Limitations:

- Single center with small sample size
- May not have captured all adverse events due to survey reporting and variation between physicians in reporting and documenting adverse events
  - Voluntary survey reporting from patients, recall bias
  - Inconsistency in GVHD reporting and scoring within EMR
- Lacks data on additional vaccines that have since received emergency use authorization (EUA)
- Retrospective, no antibody levels drawn to quantify vaccine response

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Conclusions & Clinical Application

Likely safe to administer SARS-CoV-2 vaccine to patients who have received allogeneic hematopoietic stem cell transplant, and likely that vaccination can provide these patients protection against infection with SARS-CoV-2

- Additional areas for future research
  - Prospective study with patients having had recent HCT
  - Quantify vaccine response in patients with HCT, possibly via antibody levels
  - Longer follow-up period to assess duration of response in these patients
  - Inclusion of since-released EUA vaccines

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Discussion Question

Which of the following statements best describes your mindset after reviewing this study?

a. Increases my confidence in the safety and efficacy of COVID vaccination in patients following hematopoietic stem cell transplant
b. Increases my confidence in the safety OR efficacy of COVID vaccination in patients following hematopoietic stem cell transplant
c. No change in my mindset
d. Decreases my confidence in the safety/efficacy of COVID vaccination in patients following hematopoietic stem cell transplant

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Questions?

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