REVIEW

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Efficacy of SARS-CoV-2 Vaccine Doses in Allogeneic Hemopoietic Stem Cell Recipients: A Systematic Review and Meta-Analysis

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Abstract

Objective: Recipients of allogeneic hematopoietic cell transplantation (alloHCT) are at increased risk of morbidity and mortality due to COVID-19. Immune responses to SARS-CoV-2 vaccines are blunted in these profoundly immunocompromised patients. As a result, novel strategies for protection, such as additional vaccine doses (boosters), are being explored. However, data regarding the efficacy of a third dose of SARS-CoV-2 vaccine in alloHCT recipients are limited and conflicting. **Methods:** In this systematic review and meta-analysis, we investigated the efficacy of a third dose of SARS-CoV-2 vaccine in alloHCT recipients. The review was conducted following PRISMA guidelines, and 7 studies with 385 alloHCT recipients who received 3 vaccine doses were included. The primary outcomes assessed were the rate of seroconversion following the third dose of vaccine and the rate of seroconversion in patients who did not respond to the initial 2-dose vaccination series. **Results:** The pooled humoral response rate after 3 doses of SARS-CoV-2 vaccine in alloHCT recipients was 74%. In a subgroup analysis of patients who did not respond to the initial 2-dose series, the seroconversion rate following the third vaccine dose was 49%. Notably, male patients and those with a shorter interval between alloHCT and the first vaccine dose were more likely to not respond to the third dose. **Conclusion:** In conclusion, the pooled humoral response rate of 74% following three doses of SARS-CoV-2 vaccine in alloHCT recipients highlights the potential for protection in this immunosuppressed population. Additionally, encouraging responses in nearly half of the patients who did not seroconvert with the initial 2-dose series suggest the continued utilization of additional vaccine doses until results from large prospective studies become available. These findings are critical for informing vaccination strategies in alloHCT recipients to mitigate the high mortality risk associated with COVID-19.

Keywords: AlloHCT- Viral infections- Immunocompromised- COVID-19- SARS-CoV-2 Vaccine

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Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) offers curative potential to patients with hematologic malignancies [1, 2]. However, recipients of alloHCT are at higher risk for morbidity and mortality due to COVID-19, with mortality rates of 21-32% in large scale registry studies [3, 4]. Evolving data demonstrate that immune responses to SARS-CoV-2 vaccines are blunted in these profoundly immunocompromised patients, with response rates of 69%-83% following the initial vaccination series [5, 6]. Due to the significant number of alloHCT recipients lacking an immune response to the vaccine, novel strategies for protection are being explored. Additional vaccine doses (or boosters) are promising in this regard [7]. A similar association of improved seroconversion rates has been demonstrated among cellular therapy recipients [8, 9]. However, data related to their efficacy are limited and conflicting in alloHCT setting [10-16]. In this systematic review and meta-analysis, we investigated the efficacy of a third dose of SARS-CoV-2 vaccine in alloHCT recipients.

Materials and Methods

This systematic review was conducted in accordance

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with the PRISMA guidelines. Search parameters included alloHCT patients who received 3 doses of SARS-CoV-2 vaccine. To investigate the efficacy of a third dose of vaccine, clinical and immunological data were stratified for subgroup analysis as: 1) patients with adequate antibody response (as determined by each study) following the 2-dose primary vaccination series, 2) patients with no or weak response following the 2-dose primary vaccination series. Primary outcomes were rate of seroconversion following 3 doses of vaccine, and rate of seroconversion in patients who did not respond to the primary vaccination series.

Literature searches from August 1, 2021–March 30, 2022, were reviewed from the major databases: Ovid MEDLINE, Scopus, Web of Science, Cochrane Central, medRxiv, and preprint servers. Searches were conducted by an experienced research librarian. Main search terms were hematopoietic cell transplantation, alloHCT/ allotransplant, BNT162b2/ Pfizer/ BioNTech/ Moderna, and boost/third/three/triple. Detailed search strategy and PRISMA flowchart for study selection are given in (Figure 1) and supplementary material (S1).

Articles were reviewed and the following variables were abstracted: number of patients, humoral and cellular immune response, age, gender, intervals (HCT/first vaccine dose, first/second dose, second/third dose, booster dose/humoral response assessment), previous graft vs host disease (GVHD), disease relapse, corticosteroid/IST used at the time of third dose, IgG/absolute lymphocyte count (ALC)/ CD4/CD8 before third dose, antibody assay, and vaccine type.

Risk of bias and certainty of evidence were assessed. Statistics were performed at the Medical College of Wisconsin. Humoral response data on 7 studies was imported. A Der Simonian-Laird random effects meta-analysis was performed on arcsine-transformed humoral response proportions. A formal test for heterogeneity ($Q = 36.8$, $df=6$, $p<0.0001$) suggested the presence of extra-sampling variability between the studies. Publication bias was evaluated by visual examination of the funnel plot, and a formal rank-based trend test [17].

A subgroup analysis was performed including the 3 studies that reported data in patients who had weak/no response to the primary 2-dose series. One study (Pettini) had 100% response and was not included in the analysis of the predictors of the response. The effect categorical predictors on the response to the third dose was quantified using the odds ratio and summarized using Der Simonian-Laird meta-analysis on the log-odds scale. A value of 0.5 was added to all cells when a table contained at least one 0.

The medians of the continuous predictors were summarized within response groups and compared between them using the methods of McGrath et al. [18]. This approach uses quantile regression-based meta-analysis of medians when the study results report any of the 4 combinations of summary statistics in addition to sample size: (S1) median, minimum and maximum; (S2) median, first and third quartiles; (S3) median, minimum, maximum, first and third quartiles; or (S4) mean and standard deviation. One study (Redjoul) reported mean with minimum, maximum, first and third quartiles for lymphocytes and T-cells. The median was imputed as the geometric mean of the minimum, maximum, first and third quartiles - this calculation assumes symmetry for the log-transformed variable. Note that the difference of the medians estimated among patients with positive and negative response does not equal to the difference in medians in the overall analysis, as the median is a nonlinear statistic and thus does not commute with averaging.

Results

One hundred and sixty-three (163) studies were identified via database search. Seven studies with 385 alloHCT recipients who received 3 doses of SARS-CoV-2 vaccine were included in the systematic review. Pooled humoral response rate was 74% (283/385) (95% CI, .55-.88) (Figure 2). Two hundred and thirty-five (235) of 385 patients did not seroconvert or had a weak response following the 2-dose primary series. Pooled seroconversion rate in this population was 61% following a third dose of vaccine (143/235). Patient, disease, and vaccine characteristics of alloHCT recipients who received 3 doses of SARS-CoV-2 vaccine are shown in (Table 1).

For analysis of variables associated with seroconversion, 3 studies that lacked granular data on response to a third dose of vaccine were excluded. Among the remaining 192 patients from 4 studies, seroconversion rate was 60% following a third dose of vaccine (116/192). A meta-analysis on a subgroup of patients who had not seroconverted to any degree after the initial 2-dose vaccination series demonstrated a 49% seroconversion rate with a third dose (72/146) (Table 2).

Seventy-two percent (72%) (53/74) of non-responders to the third dose were males, compared to 58% (42/72) of responders (Table 2). Non-responders were more likely to have a shorter interval between alloHCT and first vaccine dose (Table 2). Fifty-eight (58%) (43/74) of non-responders had a less than 12-month interval between alloHCT and first vaccine dose, compared to 47% (34/72) of responders (Table 2). Responders were more likely to have relapsed disease prior to the third dose [51% (38/74)] compared to responders [22% (16/72)] (Table 2).

Seventy percent (70%) (52/74) of non-responders had corticosteroid or immunosuppressive therapy (IST) usage at the time of the third dose, compared to 53% (38/72) of responders (Table 2). While the differences were not statistically significant, likely due to the small size of the study, recipients of corticosteroids or IST at the time of third dose had considerably blunted humoral vaccine response (OR = .72, 95% CI, 0.24-1.08, P = 0.07) (Table 3). All other variables in the categorical predictor model also did not yield any significant results (Table 3). Additionally, A continuous predictor model between positive and negative responders did not reveal any significant differences (Table 4).

Discussion

Vaccine responses are blunted in alloHCT patients, which likely contributes to the considerably higher

Table 1. Patient, Disease and Vaccine Characteristics of alloHCT Recipients who Received 3 SARS-CoV-2 Vaccine Doses

Study	Canti	Maillard	Redjoul	Le Bourgeois	Ram	Abid	Pettini
Total number of patients who received a 3rd dose	38	181*	42*	80	10	26	8
Humoral response after 3 vaccine doses	87% (33/38)	76% (138/181)	48% (20/42)	81% (65/80)	40% (4/10)	58% (15/26)	100% (8/8)
Humoral response after 2 vaccine doses	NR	61% (111/181)**	0	65% (52/80)	0	0	0
Cellular response after 3 vaccine doses					10/10 (100%)		
Median age, y (range)	60 (26-76)	60.5 (49.5-66.9)	59 (50-64)	57 (20-75)	66 (33-78)	69 (31-78)	65.6 (48-71)
Gender							
Males	50% (19)	61% (110)	64% (27)	56% (45)	70% (7)	73% (19)	63% (5)
Females	50% (19)	39% (71)	36% (15)	44% (35)	30% (3)	27% (7)	37% (3)
Interval between first and second dose (days)	21	30	30	NR	NR	22	NR
Interval between HCT/CT & vaccination:							
<12 months	NR	36% (65)	52% (22)	NR	30% (3)	38% (10)	37% (3)
>12 months	NR	64% (116)	48% (20)	NR	70% (70)	62% (16)	63% (5)
Median interval between 2nd dose and booster, days (range)	132 (125-153)	54 (34-73.8)	51	NR	156 (153-168)	159.5 (66-225)	180
Median interval between booster and humoral response assessment, days (range)	28	30 (27-35)	26	NR	21	38.5 (14-140)	7
Previous GVHD	29% (11)	36% (65)	60% (25)	55% (44)	80% (8)	77% (20)	13% (1)
Disease Relapse prior to booster	NR	9% (16)	24% (10)	NR	0	50% (13)	NR
Corticosteroid/IST use at the time of booster	37% (14)	43% (78)	74% (31)	24% (19)	80% (8)	35% (9)	50% (4)
Median IgG level (range) / uL < booster	152 BAU/mL***	7.2 (4.8-9.6) g/L****	NR	NR	NR	470 (82-751)	NR
Median ALC level (range) / uL < booster	NR	1.170 (.600-2.200)	NR	1.4 (.3-9.9)	NR	1.1 (.4-4.5)	NR
Median CD4 count (range) /uL < booster	NR	303 (178.5-620)	NR	NR	304 (115-704)	181.5 (76-684)	NR
Median CD8 count (range) /uL < booster	NR	NR	NR	NR	583 (150-4224)	289 (51-1795)	NR
		Abbott, Roche, DiaSorin, Siemens, Wantai					NR
Antibody Assay	Wantai		Abbott	Roche Elecsys	Abbott	Abbott	
Vaccine Type:							
•Pfizer x 3	100% (38)	98% (178)	100% (42)	100% (80)	100% (10)	69% (18)	0
•Moderna x 3	0	1% (2)	0	0	0	19% (5)	100% (8)
•Other Combination	0	1% (1)	0	0	0	12% (3)	0
Predictors of Immune Response	cGVHD and rituximab within a year of first vaccine had lower RBD Ab before not after booster	Recent HCT, immunosuppressives, and rituximab = lower Ab levels	B cell >.25 g/L at time of booster associated with better humoral response Interval between HSCT and initiation of vaccine not predictive		Longer infusion of cells was associated with better response people with B cell dysfunction		

Abbreviations: ALC, absolute lymphocyte count; IgG, immunoglobulin G; GVHD, graft-versus-host disease; IST, immunosuppressive therapy; N/A, not applicable; CAR-T, chimeric antigen receptor T-cells; BCMA, B-cell maturation antigen; [1]Median (Range); % (n); *All Ranges IQR; ** 65 strong response, 46 weak response; ***Reported in units BAU/mL, not used in meta-analysis; ****Reported in units g/L, not used in meta-analysis

COVID-19 mortality rates in HCT recipients when compared to the general population. We aimed to examine the efficacy of a third dose of SARS-CoV-2 vaccine in alloHCT recipients. In our systematic review and meta-analysis, 74% of 385 alloHCT recipients showed seroconversion after 3 doses. In a subgroup analysis of patients who did not respond after 2 doses, seroconversion rate was 49% after a third vaccine dose. Given the high mortality of COVID-19 in HCT patients, these results highlight encouraging seroconversion rates with additional

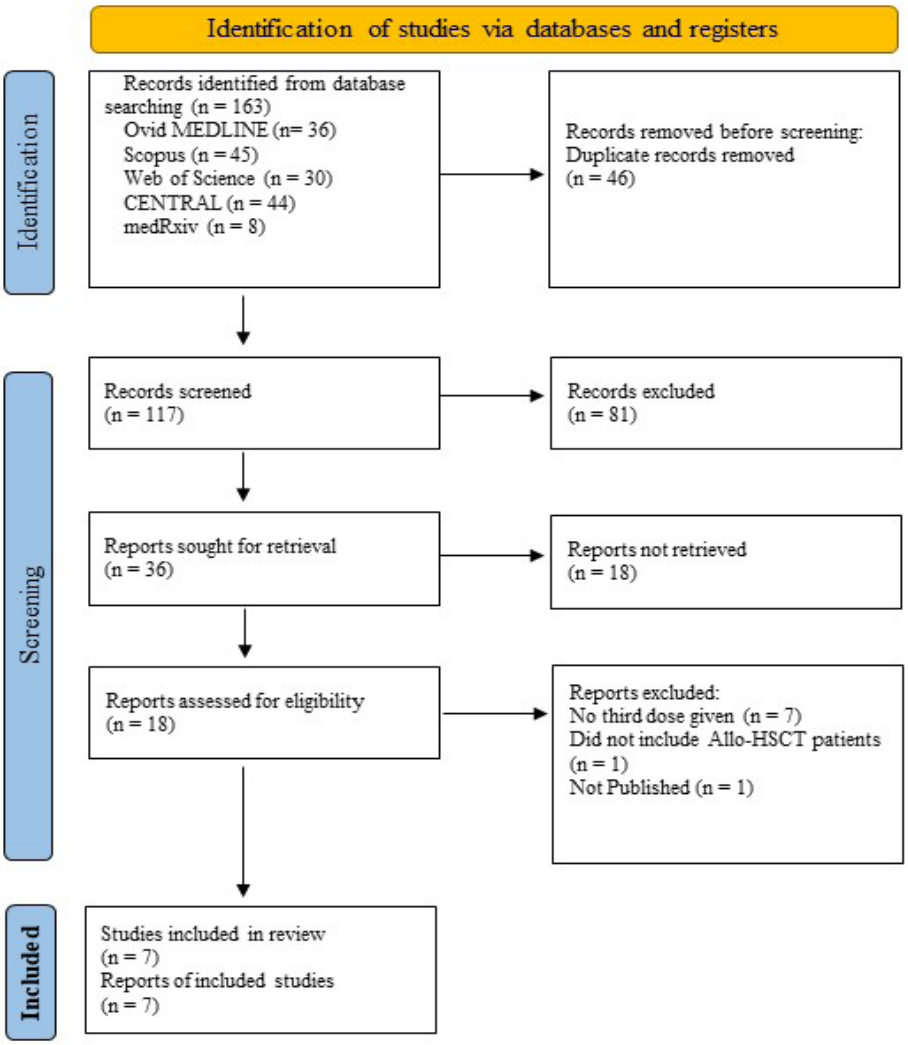

Figure 1. PRISMA Flow Diagram of Study Selection Process

doses of vaccine in initial non-responders.

Four (of the 7) studies reported data on the impact of a third vaccine dose in patients who remained seronegative after a second dose. Maillard et al. reported that 76% (138/181) of patients had a positive humoral response to a third vaccine dose. Factors that were associated with low humoral response include time-interval from HSCT <12 months, ALC 1 <g/L, immunosuppressives within

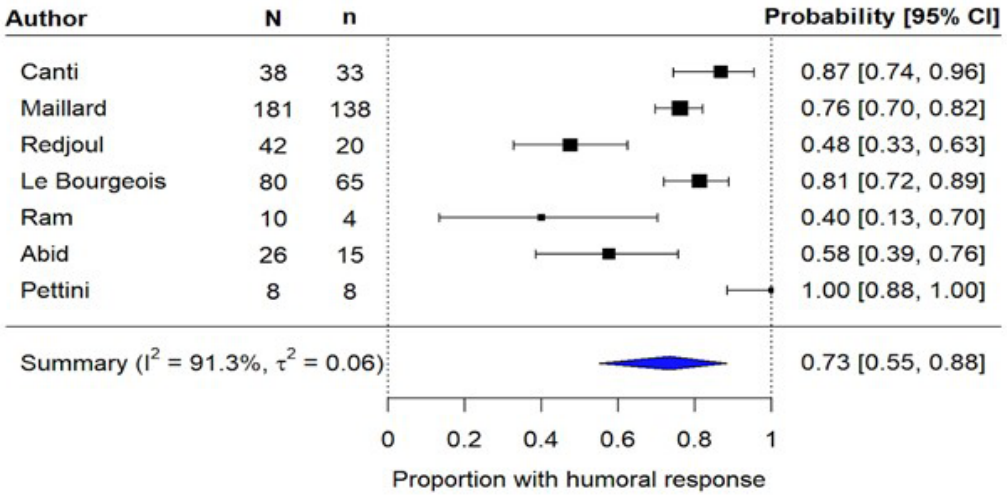

Figure 2. VA. Humoral response rates following third dose of SARS-CoV-2 vaccine. N, total number of patients; n, number of positive responders.

Table 2 . Meta-Analysis of Non-Seroconverters after Primary Vaccine Series (2-doses) who Received a Third Dose

Total number of patients with negative/weak response to 2nd dose	N=146	
Humoral immune response to third dose of vaccine (seroconversion)	+	-
	49% (72)	51% (74)
Median age, y (range)	61.6 (58-70)	61.0 (56-66)
Gender		
Males	58% (42)	72% (53)
Females	42% (30)	28% (21)
Interval between first and second dose (days)	30	30
Interval between HCT/CT & vaccination:		
<12 months	47% (34)	58% (43)
>12 months	53% (38)	42% (31)
Median interval between 2nd dose and booster, days (range)*	159 (60-180)*	110 (57-162)*
Median interval between booster and humoral response assessment, days (range)	28.5 (7-52)	30.5 (30-31)
Prior GVHD	47% (34)	51% (38)
Disease relapse prior to booster	22% (16)	51% (38)
Corticosteroid/IST use at the time of booster	53% (38)	70% (52)
Median IgG level / uL < booster	549**	439**
Median ALC level (range) / uL < booster	.823-1.1	.58-1.1
Median CD4 count (range) /uL < booster	182-226	176-176
Median CD8 count /uL < booster	170**	348**
Vaccine type:		
Pfizer x 3	80% (58)	95% (70)
Moderna x 3	17% (12)	4% (3)
Other Combination	3% (2)	1% (1)

*, This data point for the negative responder is the median of 2 numbers, while the positive responder is the median of 3 numbers; **, Only 1 study, Abid, had included data

Table 3. Subset Analysis: Categorical predictors on odds of positive response to booster dose

Predictor	# Studies	I-squared	OR	95% CI	p-value
Interval Between HCT & vaccination <12 months	3	0.00%	0.72	0.36 , 1.44	0.358
Immunosuppressive Therapy	3	0.00%	0.51	0.24 , 1.08	0.077
Male	3	42.20%	0.55	0.18 , 1.66	0.287
Pfizer	3	0.00%	0.76	0.19 , 2.97	0.688
Prior GVHD	3	0.00%	0.85	0.42 , 1.74	0.665
Relapse	3	0.00%	1.01	0.43 , 2.37	0.987

3 months of vaccination, and rituximab within 6 months of vaccination [10]. Redjoul et al. reported 48% (20/42) of patients had a positive humoral response, which was associated with B-cell count of >.25 g/L at time of third dose and IgG >1000AU/mL after second dose. Age, sex, and interval between alloHCT and first vaccination

Table 4. Subset analysis: Continuous predictors between positive and negative responders to booster dose

		Positive Response		Negative Response			Difference		
Predictor	# Studies	Median	95% CI	Median	95% CI	I-squared	Difference of Medians	95% CI	p-value
Age	3	61.64	54.18, 69.11	61.01	55.53, 66.50	6.10%	-0.34	-5.22, 4.53	0.89
ALC < Booster	3	1.1	0.73, 1.47	0.89	0.53, 1.25	0.00%	0.23	-0.08, 0.54	0.149
CD4 < Booster	2	192.64	155.71, 229.58	176	126.79, 225.21	0.00%	27.72	-71.02, 126.46	0.582
Interval Between 2nd Dose and Booster	2	108.96	11.94, 205.97	109.35	6.45, 212.24	0.00%	2.39	-10.62, 15.40	0.719
Interval Between Booster and Humoral Response Assessment	2	38.74	15.90, 61.58	30.03	28.00, 32.05	34.10%	2.5	-14.36, 19.36	0.771

were not predictive of third dose response [11]. Abid et al. reported that 58% (15/26) of patients had a positive humoral response with no statically significant differences between responders and non-responders [12]. Pettini et al. reported 100% (10/10) of patients had a positive humoral response and a significant increase of spike-specific IgG 7 days after the third dose [13].

For the 3 studies not included in the meta-analysis, Canti et al. reported 87% (33/38) of patients had a positive humoral response with 3 vaccine doses. Moderate/severe chronic GVHD was associated with lower antibody levels after the third vaccine dose. However, rituximab within 1 year before first vaccination was not associated with lower antibody levels [14]. LeBourgeois et al. reported 81% (65/80) of patients had a positive humoral response [15]. Ram et al. reported 40% (4/10) of patients with low-B cell count or complete B-cell aplasia had a positive humoral response. Longer interval between alloHCT to vaccination was associated with superior cellular response [16].

The main limitation in this review was lack of studies with data on response to a third dose of vaccine in patients who remained seronegative after their second dose, which limited the size of the meta-analyses. Additional limitations included heterogeneity in vaccine platforms, variable intervals between transplant, vaccination, and antibody assessment, and lack of data on cellular response. Further, our results may not be generalizable to recent SARS-CoV-2 variants potentially capable of evading immunity rendered by vaccinations or natural infection.

In conclusion, the pooled humoral response rate of 74% following 3 doses of SARS-CoV-2 vaccine in 385 alloHCT recipients provides a baseline for this profoundly immunosuppressed group of patients. Encouraging responses following a third dose of vaccine in nearly half of the patients who did not seroconvert with the primary 2-dose series pave the way for continued utilization of additional vaccine doses, directed against the prevalent viral variant, until results from large prospective studies become available.

Author Contribution Statement

MBA designed the study. ES, MR and MBA collected the data. AS, MR, and MBA analyzed the data. MBA wrote the first draft of the manuscript. All authors contributed to the critical revision.

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None.

Availability of data (if apply to your research)

Provided as supplementary data

Conflicts of interest

The authors declare no financial disclosures or conflicts of interest related to this work.

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