Serological responses against seasonal influenza viruses in patients with multiple myeloma treated or untreated with daratumumab after two doses of tetravalent vaccine

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Highlights

- multiple myeloma patients have poor serological responses after influenza vaccination
- treatment with daratumumab (anti-CD38) does not seem to further impair such response
- a boosted vaccination could have a positive impact on humoral responses
- future research is needed for innovative prophylaxis strategies in these patients

Serological responses against seasonal influenza viruses in patients with multiple myeloma treated or untreated with daratumumab after two doses of tetravalent vaccine.

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ABSTRACT (200/200)

Objectives

Daratumumab-treated myeloma patients may face increased seasonal influenza risk due to weakened post-vaccination immune responses, especially with daratumumab treatment. We aimed to assess humoral responses to boosted influenza vaccination in daratumumab-treated or -untreated patients.

Methods

In a single-center study, we evaluated humoral responses (hemagglutination-inhibition assay) one month following a two-injection (4-weeks apart) influenza vaccination (standard dose) in 84 patients with multiple myeloma (40 with daratumumab in the past year).

Results

Seroprotection rates (titer ≥1/40) after the second vaccine injection were low across vaccinal subtypes (except for A-H3N2): 71.3% (A-H3N2), 19.7% (A-H1N1pdm09), 9.9% (B-Victoria), 11.3% (B-Yamagata). Only A-H3N2 seroprotection rates significantly increased with the booster in daratumumab-treated patients (30% (12/40) after one injection vs. 55% (22/40) after the boost; p=0.01).

After propensity score weighting, daratumumab was not significantly associated with a reduced likelihood of seroprotection against at least one vaccine strain (OR 0.65 [95% CI: 0.22–1.88]).

Conclusion

While daratumumab treatment did not lead to a significant reduction in seroprotection rates following influenza vaccination, a booster vaccine injection demonstrated potential benefit for specific strains (A-H3N2) in patients undergoing daratumumab treatment. Nevertheless, the overall low response rates in patients with multiple myeloma necessitates the development of alternative vaccination and prophylaxis strategies.

Keywords: influenza; multiple myeloma; vaccine; daratumumab

Introduction

Multiple myeloma (MM), a prevalent malignancy, heightens infection susceptibility in patients due to several factors including age-related immune senescence, altered immunoglobulin production, and treatment-induced immunosuppression[1]. Overall, patients with MM have a 7 to 10-fold increased risk of bacterial or viral infection, resulting in 50% of premature deaths caused by an opportunistic infection[2], including seasonal influenza viruses[3].

While IDSA do not recommend vaccination in patients receiving intensive chemotherapy or anti-B cell antibodies[4] due to low immune responses[5]; European guidelines recommend a booster vaccine a month later after the initial vaccination, despite relying on weak evidence[6].

The rapidly evolving nature of the therapeutic field poses a significant challenge to establishing a practical vaccination strategy. Therefore, it is crucial to consistently provide updated data to guide clinicians in advising patients undergoing these innovative therapeutics.

Daratumumab has experienced a remarkable surge in usage for MM in recent years, as it is now a recommended frontline therapy[7]. A recent insightful exploratory study revealed that despite daratumumab's ability to induce lysis in healthy plasma cells expressing CD38, these patients did not exhibit a significantly lower response after a single shot of trivalent influenza vaccine (17-25% seroprotection, consistent with existing literature). However, the study was limited by a small sample size (n=13).

Here, we designed a prospective study evaluating serological responses after a boosted vaccination strategy among patients with multiple myeloma treated with daratumumab.

Methods

We conducted a prospective, single-center cohort study evaluating serological responses among patients treated for MM in a tertiary center. All patients actively treated in our center were offered to participate in a prospective cohort investigating the recommended seasonal flu boosted vaccination strategy for the 2019/2020 season (two quadrivalent vaccine injections (Influvac Tetra, 15 µg HA for each strain) 28 days (±4) apart). Humoral response was evaluated by hemagglutinin inhibition assays (HI) 28 days after each vaccine injection (± 5 days, referred here as M1 and M2 timepoints). Specific timing guidance for vaccination in relation to ongoing treatment was not enforced. Seroprotection was defined as a HI titer ≥1/40.

To address potential confounding by indication bias, treatment-groups comparison was performed using a propensity score-based standardized mortality ratio (SMR) weighting. Propensity score was estimated by a multivariable logistic model. The study was approved by local ethics committee (CPP EST III – 11/09/2018) and in accordance with the 1964 Helsinki Declaration. Additional details regarding immunological response evaluation, statistics, and ethics are available in the Appendix S1.

Results

Overall, the study included 84 patients (40 treated by Daratumumab in the last 12 months, including 29 the day of vaccination). Baseline characteristics are shown in **Table 1**. Briefly, included patients were predominantly male (52/85, 61%), with a median age of 68 years old

(95% IQR [56; 74]). Daratumumab-treated patients had received significantly more previous lines of treatment (3 [2; 4] vs 2 [1; 2], p<0.001). Reflecting standard practice at the time of the study, treatment indication was aligned with on-going and recently published trials, resulting in more proteasome inhibitors used in the group of daratumumab-treated patients and a longer time since autologous hematopoietic stem cell transplantation (HSCT)(p<0.001).

A total of 71 patients received both vaccine injections and had serum available at baseline and a month after each vaccine injection. At baseline, a low detectable titer was found in 58/71 patients against A-H3N2 (82%), 23/71 against A-H1N1pdm09 (32%), 9/71 against B-Victoria (13%), 1/71 against B-Yamagata (1%) (**Supplementary Figure 1**). In univariate analysis, there was no observed association between daratumumab treatment, therapeutic agents utilized, or serum gammaglobulin levels with lower titer at M2. Notably, the sole variable linked to a reduced titer at M2 was autologous HSCT within a year. The limited sample size of our study precluded us from conducting multivariate analysis without risking overfitting of the results.

The most robust immune response was observed against A-H3N2 subtype (**Supplementary Figure 2**). Seroprotection rates were not significantly different at any time point between patients who received daratumumab and those who did not (**Figure 1**, **Table 1**). Regarding A-H3N2, the second vaccination (M2) markedly raised seroprotection rates in daratumumab-treated patients (12/40, 30% to 22/40, 55%; p=0.013), but showed no significant increase in those not receiving daratumumab (23/44, 52.3% to 29/44, 65.9%; p=0.15) (**Figure 1**). Notably, although some patients treated with daratumumab exhibited a robust response against A-H3N2 (multiple dilutions beyond seroprotection levels (titer >1/40: 9/40, 22.5%)), only one patient

developed such a response against A-H1N1pdm09 which was only transient (undetectable after the second vaccine injection) (**Figure 1, Supplementary Figure 1**).

The booster (M2) did not lead to an increase in strain coverage (p=0.78), with only 20/71 patients who developed seroprotection against more than one strain (**Supplementary Figure 2**).

To address potential confounding by indication, we assessed the impact of daratumumab treatment on the probability of achieving seroprotection against at least one vaccine strain in the standardized mortality ratio weighted population. In this analysis, daratumumab showed no significant association with a reduced likelihood of developing such seroprotection (OR 0.65 [95% CI: 0.22–1.88]).

Discussion

To our knowledge, this prospective cohort represents the largest series to date assessing the impact of daratumumab on a reinforced influenza vaccination strategy in patients with MM. Overall, the seroprotection rates across the vaccine strains were limited, and the range of strains encompassed by post-vaccinal responses remained narrow, irrespective of daratumumab treatment.

A previous study reported higher response rates after a boosted vaccination in patients with MM [8], but their study included untreated patients and used high-dose vaccines (vs standard

hemagglutinin dose in ours), which suggests that higher dose vaccines should be evaluated in the future.

We observed the most robust response against the A-H3N2 subtype, against which a booster vaccine was able to significantly increase seroprotection rates in daratumumab-treated patients.

The only factor associated with reduced GMT after vaccination was having received an autologous-HSCT within the past year, which was more frequent in the non-daratumumab-treated group, potentially masking a detrimental effect of daratumumab (which reduced post-vaccination antibody concentrations against SARS-CoV-2)[9].

Clinical protection assessment in our cohort was hindered by the limited recorded events during the 2019/2020 influenza season, impacted by the COVID-19 pandemic (a shorter season in France, spanning 9 weeks, and lockdowns reducing in-person contacts).

Our study has limitations. First, we lacked comprehensive data on prior influenza vaccinations, crucial for understanding pre-existing immunity. Second, it was conducted in a single season with limited participants, leading to wide confidence intervals and hindering conclusive findings on daratumumab's impact on seroprotection. However, a booster vaccine showed potential benefits. Third, unmeasured confounders might persist despite SMR weighting. Notably, lymphocyte subpopulations (NK, T, B cells) counts were unavailable, limiting detailed correlations. Finally, the widely used correlation between clinical protection and HIA titers

≥1/40 was established in young healthy adults[10], and it remains unknown if such correlate holds among a highly heterogeneous population as immunocompromised patients.

In conclusion, our study found no reduced response to influenza vaccine in daratumumab-treated patients and suggested a potential benefit of an influenza booster vaccine. This supports a two-injections vaccination strategy given the widespread use of daratumumab. However, it may not offer broad protection against all circulating subtypes, underscoring the need for future studies to assess high dose boosted vaccination or passive immunoprophylaxis in MM patients on novel immunotherapies.

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Simon B. Gressens designed and performed the research, analyzed the data and wrote the first draft of the manuscript. Vincent Enouf contributed essential reagents or tools and performed biological analysis. Antoine Créon analyzed the data and performed statistical analysis. Giovanna Melica, Francois Lemonnier, Jehan Dupuis, Taoufik El Gnaoui, Mohammad Hammoud, Karim Belhadj, Corinne Haioun, Anne Le Bouter performed the research. Sebastien Gallien, Fabien Le Bras, Slim Fourati designed the study and ensured the coordination between the different involved departments. All authors commented and corrected the manuscript before agreeing on the final version.

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Conflicts of interest

F. Lemonnier received research funding from Institut Roche and travel grant from Gilead,

G. Melica received honoraria from lectures from Astellas, Pfizer, Gilead, MSD, Janssen.

S. Fourati received research grants from Moderna, and consulting fees from Moderna, Astrazeneca, Pfizer, GSK and Cepheid, as well as support for traval from Astellas, Gilead and Pfizer.

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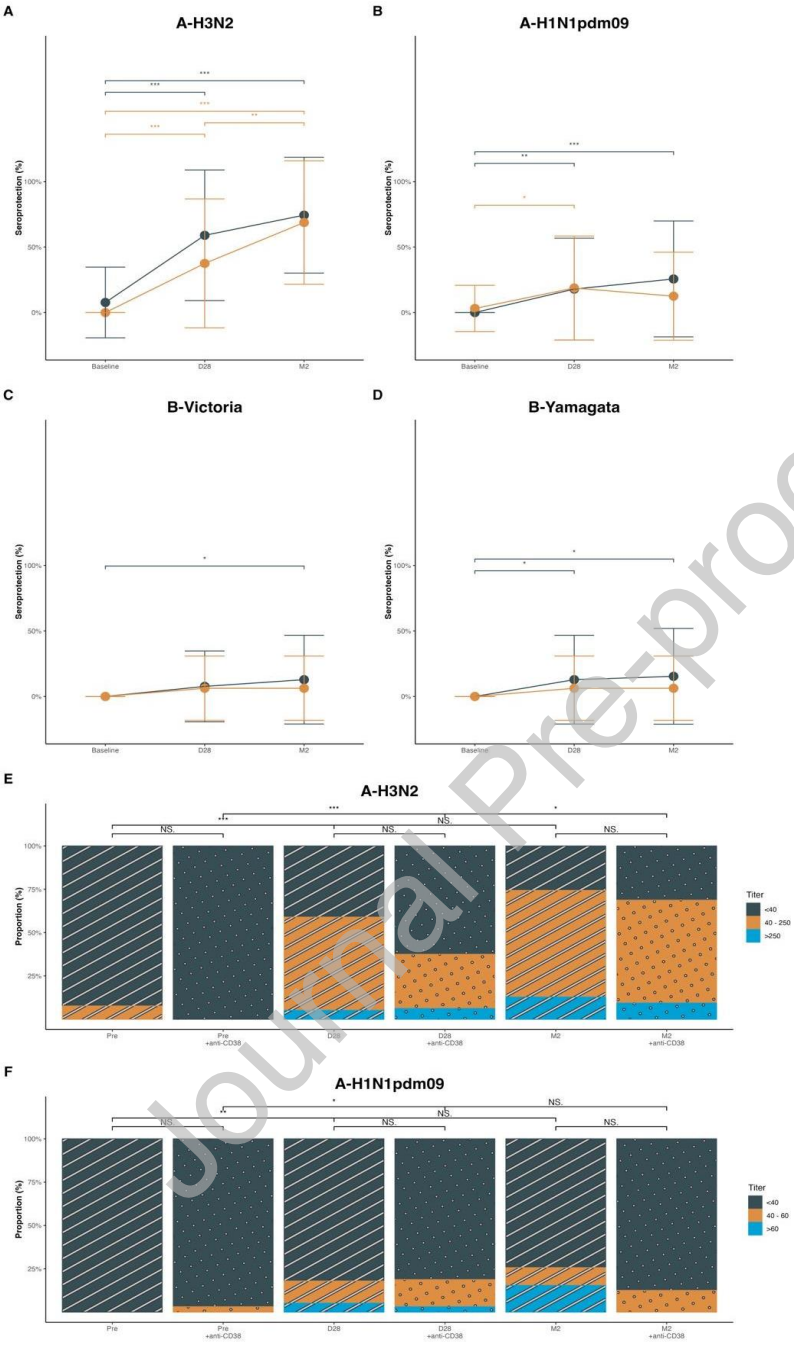
Figure 1. Seroprotection levels in the different treatment groups



Seroprotection was defined as a measured titer ≥1/40 (immune-agglutination assay, IHA) against a specific strain**. Panels A-D**. Seroprotection rates against the four vaccine subtypes at baseline and after each vaccine injection in patients who received Daratumumab in the last 12

months (depicted by the golden curve) or those not receiving such treatment (depicted by the black curve). **Panels E and F**. Proportion of patients achieving different levels of serological titers after each vaccine injection against type A subtypes. Titers categories are color-coded. Patients with a history of Daratumumab use in the past 12 months are represented with dotted bars, while patients not receiving such treatment are depicted with striped bars. Differences are considered significant when p-value < 0.05. *: p-value <0.05, **: p-value <0.01, ***: p-value <0.001.

Table 1. Patient characteristics & seroprotection rates

		Anti-CD38 in the last 12-months		
	Total (N=84)	**No (N=44)**	**Yes (N=40)**	**P-value**
Gender (Female, %)	33 (39 %)	18 (41 %)	15 (38 %)	0.92
Age (years)	68 (56 - 74)	61 (56 - 72)	72 (61 - 76)	0.15
Multiple Myeloma Isotype (%)				1
IgG	45 (54 %)	24 (55 %)	21 (52 %)	
Non-IgG	39 (46 %)	20 (45 %)	19 (48 %)	
Light chain Isotype (%)				0.80
Kappa	52 (62 %)	28 (64 %)	24 (60 %)	
Lambda	31 (37 %)	15 (34 %)	16 (40 %)	

		Anti-CD38 in the last 12-months		
	Total (N=84)	**No (N=44)**	**Yes (N=40)**	**P-value**
R-ISS	2.0 (1.0 - 2.3)	2.0 (1.8 - 2.3)	2.0 (1.0 - 2.3)	0.87
Seric gammaglobulins at vaccination (g/L)	4.0 (2.9 - 5.6)	4.5 (3.1 - 6.2)	3.8 (2.6 - 5.2)	0.29
Current IgIV supplementation (%)	9 (11 %)	4 (9.1 %)	5 (12 %)	0.88
Number of previous relapses (n)	2.0 (1.0 – 3.0)	1.0 (1.0 – 2.0)	3.0 (2.0 – 3.0)	**<0.001**
Duration of active disease (years)	2.0 (1.0 – 5.3)	1.0 (1.0 – 4.0)	4.0 (2.0 – 6.3)	**<0.001**
Number of previous therapeutic lines (n)	2.0 (1.0 - 3.0)	2.0 (1.0 - 2.0)	3.0 (2.0 - 4.0)	**<0.001**
History of autologous-HSCT (%)	39 (46 %)	24 (55 %)	15 (38 %)	0.12
Autologous-HSCT to vaccination (days)	370 (140 - 1100)	200 (84 - 380)	1500 (760 - 2600)	**<0.001**
IMWG status at vaccination (%)				0.07
≥VGPR	44 (52 %)	28 (64 %)	16 (40 %)	
Partial response / stable	26 (31 %)	10 (23 %)	16 (40 %)	

		Anti-CD38 in the last 12-months		
	Total (N=84)	**No (N=44)**	**Yes (N=40)**	**P-value**
disease				
Progressive disease	13 (15 %)	5 (11 %)	8 (20 %)	
Lymphocyte count at vaccination (10^9/L)	0.94 (0.68 - 1.4)	0.93 (0.69 - 1.3)	0.99 (0.63 - 1.5)	0.78
Therapeutic lines at vaccination				
Proteasome inhibitors (%)	42 (50 %)	9 (20 %)	33 (82 %)	**<0.001**
Alkylating agents (%)	13 (15 %)	11 (25 %)	2 (5 %)	**0.01**
Immunomodulators (%)	59 (70 %)	30 (68 %)	29 (72 %)	0.67
BCL2 inhibitor (%)	5 (6 %)	1 (2 %)	4 (10 %)	0.14
Steroids (%)	72 (86 %)	36 (82 %)	36 (90 %)	0.291
Anti-CD38 antibody[1] (%)	34 (40 %)	0 (0 %)	34 (85 %)	**<0.001**
Last anti-CD38 administration				
Same day as vaccination	-	-	29 (72%)	-
1 – 31 days before vaccination	-	-	5 (12%)	-
32 – 365 days before vaccination	-	-	6 (15%)	-
Seroprotection rates (HIA titer ≥1/40)				
A-H1N1pdm09				

			Anti-CD38 in the last 12-months		
		Total (N=84)	**No (N=44)**	**Yes (N=40)**	**P-value**
	Baseline (%)	1 (1.4%)	0 (0%)	1 (2.5%)	0.33
	D28 (%)	13 (18.3%)	7 (15.9%)	6 (15%)	0.93
	M2 (%)	14 (19.7%)	10 (22.7%)	4 (10%)	0.16
A-H3N2					
	Baseline (%)	3 (4.2%)	3 (6.8%)	0 (0%)	0.08
	D28 (%)	35 (49.3%)	23 (52.3%)	12 (30%)	0.07
	M2 (%)	51 (71.8%)	29 (65.9%)	22 (55%)	0.61
B-Victoria					
	Baseline (%)	0 (0%)	0 (0%)	0 (0%)	-
	D28 (%)	5 (7%)	3 (6.8%)	2 (5%)	0.82
	M2 (%)	7 (9.9%)	5 (11.4%)	2 (5%)	0.35
B-Yamagata					
	Baseline (%)	0 (0%)	0 (0%)	0 (0%)	-
	D28 (%)	7 (9.9%)	5 (11.4%)	2 (5%)	0.35
	M2 (%)	8 (11.3%)	6 (13.6%)	2 (5%)	0.22

[1] 6 patients underwent Daratumumab therapy within a year of vaccination, although they were on a different therapeutic regimen at the time of vaccination.

HSCT : hematopoietic stem cell transplantation. Baseline, D28 and M2 indicate pre-vaccination, 28 days (±5 days) after the first vaccination and 28 days (±5 days) after the second vaccination respectively. P-value < 0.05 (two-sided) are considered significative. All presented comparisons are between groups receiving/not receiving daratumumab.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *[Journal name]* and was not involved in the editorial review or the decision to publish this article.

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